

THE ARCHIVES OF INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago	
RICHARD C. CABOT, Boston	THEO. C. JANEWAY, Baltimore
GEORGE DOCK, St. Louis	WARFIELD T. LONGCOPE, New York City
W. S. THAYER, Baltimore	

VOLUME XX

1917

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

TO SUBSCRIBERS

Help Us To Economize

The expenses connected with printing and publishing The Archives have greatly increased. In addition to the increase in cost of paper, supplies and labor, the first class postage rates have been increased 50 per cent.

The Archives carries no advertising and is, therefore, dependent on its subscription income alone. Economy is necessary in order to maintain the present high standard of The Archives, and a big item of expense can be eliminated if subscribers will remit without waiting to receive a special bill.

No regular bills will be sent on January 1, as heretofore, but instead a remittance slip is inserted in this issue. If every subscriber will remit voluntarily and promptly, it will mean a substantial saving.

The rates are as follows:

<i>Archives alone.....</i>	<i>\$ 1.00</i>
<i>Journal A. M. A. and Archives combined..</i>	<i>8.00</i>

The cooperation of the subscribers will be appreciated, and it is hoped that they will remit promptly.

CONTENTS OF VOLUME XX

JULY, 1917. NUMBER 1

	PAGE
THE PULSE FLOW IN THE BRACHIAL ARTERY. V. THE INFLUENCE OF CERTAIN DRUGS. ALBION WALTER HEWLETT, M.D., SAN FRANCISCO.....	1
STUDY OF A CASE OF DIABETES INSIPIDUS WITH SPECIAL REFERENCE TO THE MECHANISM OF THE DIURESIS AND OF THE ACTION OF PITUITARY EXTRACT ON IT. C. D. CHRISTIE, M.D., AND G. N. STEWART, M.D., CLEVELAND..	10
MULTIPLE HEMANGIOMAS OF THE SKIN ASSOCIATED WITH DYSPIUITARISM. GEORGE DOUGLAS HEAD, B.S., M.D., MINNEAPOLIS.....	24
PHTHISIS PULMONALIS AND OTHER FORMS OF INTRATHORACIC TUBERCULOSIS. W. A. GEKLER, M.D., CHICAGO.....	32
THE STUDY OF A SMALL OUTBREAK OF POLIOMYELITIS IN AN APARTMENT HOUSE, OCCURRING IN THE COURSE OF AN EPIDEMIC IN A LARGE CITY. MONTROSE T. BURROWS, M.D., AND EDWARDS A. PARK, M.D., BALTIMORE	56
THE INFLUENCE OF SPLENECTOMY ON METABOLISM IN ANEMIA. W. DENIS, BOSTON	79
THE ELECTROCARDIOGRAM; ITS RELATION TO CARDIODYNAMIC EVENTS. CARL J. WIGGERS, M.D., NEW YORK.....	93
STUDIES OF THE BLOOD IN BERIBERI. I. YOSHIKAWA, K. YANO AND T. NEMOTO, TOKYO, JAPAN.....	103
A STUDY OF RENAL FUNCTION IN PATIENTS CONVALESCING FROM ACUTE FEVERS. ARTHUR BOOKMAN, M.D., NEW YORK.....	112
HEART BLOCK ASSOCIATED WITH HIGH BLOOD PRESSURE. JOHN H. MUSSER, JR., M.D., PHILADELPHIA.....	127
STUDIES IN THE VARIATIONS OF THE TONUS OF THE GASTRIC MUSCULATURE IN HEALTH AND DISEASE. BURRILL B. CROHN, M.D., AND ABRAHAM O. WILENSKY, M.D., NEW YORK.....	145

AUGUST, 1917. NUMBER 2

	PAGE
AN ERROR IN THE ELECTROCARDIOGRAM ARISING IN THE APPLICATION OF THE ELECTRODES. HAROLD E. B. PARDEE, M.D., NEW YORK.....	161
STUDIES IN PROTEIN INTOXICATION. I. BLOOD COAGULATION. HOWARD F. SHATTUCK, M.D., NEW YORK.....	167
EMETIN DIARRHEA—CLINICAL AND EXPERIMENTAL. A. R. KILGORE, M.D., AND J. H. LIU, M.D., SHANGHAI, CHINA.....	178
STUDIES ON THE OXIDASE REACTION OF THE CELLS IN NORMAL AND LEUKEMIC BLOOD. N. ROSENTHAL, M.D., NEW YORK.....	184
RELATION OF PELLAGRA TO LOCATION OF DOMICILE IN SPARTAN MILLS, S. C., AND THE ADJACENT DISTRICT. J. F. SILER, M.D., P. E. GARRISON, M.D., AND W. J. MACNEAL, M.D., NEW YORK.....	198

CONTENTS OF VOLUME XX

ARCH. IN

SEPTEMBER, 1917. NUMBER 3

	PAGE
THE ETIOLOGIC AGENT OF RAT BITE DISEASE. PRELIMINARY REPORT. J. KITAGAWA, M.D., AND T. MUKOYAMA, M.D., NAGOYA, JAPAN.....	317
THE SALICYLATES. VIII. SALICYL EDEMA. P. J. HANZLIK, M.D., R. W. SCOTT, M.D., AND J. L. REYCRAFT, M.D., CLEVELAND.....	329
A STUDY OF POLIOMYELITIS. REPORT OF THE WORK OF THE MENINGITIS DIVISION OF THE RESEARCH LABORATORY IN THE 1916 EPIDEMIC. JOSEPHINE B. NEAL, M.D., HARRY L. ABRAMSON, M.D., AND ASSOCIATES, NEW YORK	341
FURTHER STUDIES WITH THE SCHICK TEST. ABRAHAM ZINGHER, M.D., NEW YORK	392
THE EFFECT OF UNDERNUTRITION ON MUSCULAR FORCE. A STUDY OF THE INFLUENCE OF LOW DIETS, OR THE ALLEN METHOD OF TREATMENT, ON THE PHYSICAL VIGOR OF DIABETICS. JOHN R. WILLIAMS, M.D., ROCHESTER, N. Y.....	399
AURICULAR FLUTTER. A CONSIDERATION OF SOME PROBLEMS ARISING IN THE STUDY OF A CASE, AND OF THE LITERATURE. JAMES D. HEARD, M.D., PITTSBURGH, AND ARTHUR E. STRAUSS, S.B., M.D., ST. LOUIS.....	409
CLINICAL STUDIES ON THE RESPIRATION. III. A MECHANICAL FACTOR IN THE PRODUCTION OF DYSPNEA IN PATIENTS WITH CARDIAC DISEASE. FRANCIS W. PEABODY, M.D., BOSTON.....	433
CLINICAL STUDIES ON THE RESPIRATION. IV. THE VITAL CAPACITY OF THE LUNGS AND ITS RELATION TO DYSPNEA. FRANCIS W. PEABODY, M.D., AND JOHN A. WENTWORTH, M.D., BOSTON.....	443
CLINICAL STUDIES ON THE RESPIRATION. V. THE BASAL METABOLISM AND THE MINUTE-VOLUME OF THE RESPIRATION OF PATIENTS WITH CARDIAC DISEASE. FRANCIS W. PEABODY, M.D., JOHN A. WENTWORTH, M.D., AND BERTHA I. BARKER, BOSTON.....	468
BOOK REVIEWS:	
A MONOGRAPH ON THE EPIDEMIC OF POLIOMYELITIS (INFANTILE PARAL- YSIS) IN NEW YORK CITY IN 1916.....	479
THE DIAGNOSIS AND TREATMENT OF MYOCARDIAL FUNCTION, WITH SPECIAL REFERENCE TO THE USE OF GRAPHIC METHODS. BY L. STUART HART, A.M., M.D.....	480

OCTOBER, 1917. NUMBER 4

	PAGE
A STUDY OF URIC ACID IN GOUT. C. W. McCLURE, M.D., AND J. H. PRATT, M.D., BOSTON.....	481
THE FERMENT-ANTIFERMENT BALANCE AND ITS RELATION TO THERAPEUSIS. W. F. PETERSEN, M.D., CHICAGO.....	515
THE RELATION OF PELLAGRA TO LOCATION OF DOMICILE IN INMAN MILLS, INMAN. S. C. J. F. SILER, M.D., P. E. GARRISON, M.D., AND W. J. MACNEAL, M.D., NEW YORK.....	521
THE ABSORPTION OF PHENOLSULPHONEPHTHALEIN FROM THE SUBARACHNOID SPACE IN DISEASES OF THE CENTRAL NERVOUS SYSTEM. H. G. MEHRTENS, M.D., AND H. F. WEST, M.D., SAN FRANCISCO.....	575
A STUDY OF THE ERYTHROCYTES IN A CASE OF SEVERE ANEMIA WITH ELONGATED AND SICKLE-SHAPED RED BLOOD CORPUSCLES. V. E. EMMEL, PH.D., CHICAGO	586

OCTOBER—Continued

	PAGE
REMARKS ON THE CHOLESTEROL CONTENT OF HUMAN BLOOD. F. D. GORHAM, M.D., ST. LOUIS, AND V. C. MYERS, PH.D., NEW YORK.....	599
THE TEMPERATURE METHOD IN THE LOCALIZATION OF A CARDIAC PACE-MAKER. B. H. SCHLOMOVITZ, M.S., CHICAGO, AND C. S. CHASE, M.D., IOWA CITY, IOWA.....	613
PYOPNEUMOTHORAX AND PNEUMOTHORAX. A REPORT OF TWO CASES WITH INTERESTING CLINICAL AND ROENTGENOLOGIC FINDINGS. J. A. HONEIJ, M.D., NEW HAVEN, CONN.....	629
ASTHMA COMPLICATING THE SERUM TREATMENT OF PNEUMONIA. H. L. ALEXANDER, M.D., BOSTON.....	636

NOVEMBER, 1917. NUMBER 5

	PAGE
THE RENAL FUNCTION IN GOUT. C. W. MCCLURE, M.D., BOSTON.....	641
AMYOTONIA CONGENITA OF OPPENHEIM. A REPORT OF SIX CASES, WITH A FULL REVIEW OF THE LITERATURE. MARK S. REUBEN, M.D., NEW YORK	657
DIAGNOSTIC SIGNS FROM THE SCALENI, INTERCOSTAL MUSCLES AND THE DIAPHRAGM IN LUNG VENTILATION. C. F. HOOVER, M.D., CLEVELAND....	701
SERUM CHANGES FOLLOWING PROTEIN "SHOCK" THERAPY. WILLIAM F. PETERSEN, M.D., CHICAGO.....	716
VENTRICULAR FIBRILLATION IN MAN WITH CARDIAC RECOVERY. G. CANBY ROBINSON, M.D., AND J. F. BREDECK, M.D., ST. LOUIS.....	725
LOCALIZED AND INTERLOBAR PNEUMOTHORAX COMPLICATING PULMONARY TUBERCULOSIS. MAURICE FISHBERG, M.D., NEW YORK.....	739
STUDIES ON BLOOD SUGAR. LOUIS HAMMAN, M.D., AND I. I. HIRSCHMAN, M.D., BALTIMORE.....	761
OBSERVATIONS ON KIDNEY FUNCTION IN DIABETES MELLITUS. R. FITZ, M.D., NEW YORK.....	809
BOOK REVIEW: PATHOGENIC MICRO-ORGANISMS. WILLIAM HALLOCK PARK, M.D., AND ANNA WESSELS WILLIAMS, M.D., ASSISTED BY CHARLES KRUMWEIDE, JR., M.D.....	828

DECEMBER, 1917. NUMBER 6

	PAGE
STUDIES OF THE HEART'S FUNCTIONAL CAPACITY. THEODORE B. BARRINGER, JR., M.D., NEW YORK.....	829
FIVE GENERATIONS OF ANGIONEUROTIC EDEMA. JOSEPH R. CROWDER, M.D., SULLIVAN, IND., AND THOMAS R. CROWDER, M.D., CHICAGO.....	840
EXPERIMENTAL HYDRONEPHROSIS. FUNCTIONAL AND ANATOMIC CHANGES IN THE KIDNEY FOLLOWING PARTIAL URETERAL OBSTRUCTION. N. M. KEITH, M.D., AND D. S. PULFORD, JR., M.D., BALTIMORE.....	853
THE NONPROTEIN CONSTITUENTS OF EDEMA FLUIDS. W. DENIS, PH.D., WITH THE ASSISTANCE OF A. S. MINOT, A.B., BOSTON.....	879
A CASE OF CANTHARIDES POISONING WITH SPECIAL REFERENCE TO THE BLOOD PICTURE. SAMUEL T. LIPSITZ, M.D., AND A. J. CROSS, M.D., ST. LOUIS	889

CONTENTS OF VOLUME XX

ARCH: INT

DECEMBER—Continued

	PAGE
THE EFFECT OF PANCREATECTOMY ON THE CATALASE CONTENT OF THE TISSUES. J. KENNEDY, A.B., CHICAGO, AND W. E. BURGE, A.B., A.M., PH.D., URBANA, ILL.....	892
THE IRON METABOLISM OF HEMOCHROMATOSIS. C. P. HOWARD, M.D., AND F. A. STEVENS, M.D., IOWA CITY, IOWA.....	896
POLYCYTHEMIA INDUCED BY TINCTURE OF CANTHARIDES. PRELIMINARY REPORT. SAMUEL T. LIPSITZ, M.D., A. L. FUERTH, M.D., AND A. J. CROSS, M.D., ST. LOUIS.....	913
OBSERVATIONS ON ACUTE MERCURIC CHLORID NEPHROSIS. WITH A REPORT OF TWO CASES. WALTER R. CAMPBELL, M.A., M.D., TORONTO, CANADA..	919
STUDIES ON ACIDOSIS. THE IMMEDIATE CAUSE OF DEATH, AND REMARKS ON THE ACIDOSIS OF NEPHRITIS. JAMES L. WHITNEY, M.D., SAN FRANCISCO	931
A REPORT ON FORTY CASES OF ACUTE ARTHRITIS TREATED BY THE INTRAVENOUS INJECTION OF FOREIGN PROTEIN. RUSSELL L. CECIL, M.D., NEW YORK	951
BLOOD SUGAR IN HYPERTHYROIDISM. W. DENIS, PH.D., AND J. C. AUB, M.D., WITH THE ASSISTANCE OF A. S. MINOT, A.B., BOSTON.....	964

THE PULSE FLOW IN THE BRACHIAL ARTERY

V. THE INFLUENCE OF CERTAIN DRUGS *

ALBION WALTER HEWLETT, M.D.

SAN FRANCISCO

GENERAL CONSIDERATIONS

By methods which have been described elsewhere¹ we are able to determine (a) the average blood flow in the arm of man over brief periods of time, (b) the volume and form of the pulse wave entering the arm, and (c) the blood flow in the main arm arteries during each portion of the pulse cycle. The last, which we have called the pulse flow in the brachial artery, may be recorded directly. It is, however, a resultant of the two preceding components; that is, of the average blood flow and of the variations in this flow produced by the entrance of the pulse wave into the arm.

The average rate of blood flow in the arm depends in part on the average blood pressure, and in part on the local resistance opposed to the flow of blood through the smaller arteries and capillaries of the arm. By the method which we have used this average blood flow varies considerably even in a single individual, apparently because the body temperature is being constantly regulated by alterations in the rate of blood flow through its peripheral tissues. Even when we have made some effort to maintain a relatively constant external temperature we have at times encountered gradual changes in the rate of arm circulation. For this reason we have not been able to draw conclusions as to the effect of drugs on this rate unless the changes observed were marked and constant.²

* Submitted for publication Feb. 1, 1917.

* From the Department of Internal Medicine, University of Michigan.

1. Hewlett, A. W., and van Zwaluwenburg, J. G.: The Pulse Flow in the Brachial Artery. I. Technic and General Considerations, *THE ARCHIVES INT. MED.*, 1913, **12**, 1.

2. G. N. Stewart (Studies on the Circulation in Man. I. The Measurement of the Blood Flow in the Hands, Heart, 1911, **3**, 33) found, on the contrary, a rather constant rate of blood flow through the hand for any given individual. In the method which he used the hand is immersed in water of a relatively constant temperature. Possibly this may exercise a steadying influence on the local blood flow.

The volume and form of the pulse wave entering the arm depend on a complex interaction of many factors. Among these are the size and duration of the ventricular output and the condition of the large and small arteries, not only in the arm itself, but in important vascular areas elsewhere. An adequate physical explanation of changes in the volume and form of the pulse does not seem possible at the present time. In the present paper, therefore, I propose merely to record some observations in which the pulse flow in the arm was determined before and after the administration of certain drugs in therapeutic doses.

Nitroglycerin.—The changes which follow the placing of one or two drops of a 1 per cent. solution of nitroglycerin on the tongue have been described in a previous paper.³ These consist of: (1) a swelling of the arm; (2) an increase in the size of the volume pulse; (3) a change toward a more pointed or collapsing pulse; (4) the disappearance of the smaller secondary waves, and (5) no marked or constant alteration in the rate of blood flow through the arm. These typical pulse changes usually begin in two or three minutes, reach their maximum in five or six minutes and pass off in about fifteen minutes. A considerable number of observations, fifty or more, have shown the constancy of these changes in normal young adults. In chronic arterial hypertension, similar changes may also be produced, although not so readily as in young adults. It is noteworthy that the pulse changes in such patients may occur, even when the blood pressure, though reduced, is still far above the normal.

Inasmuch as it seemed probable that these changes might be due in part to a reduction in the elastic coefficient of the larger arm arteries, and that such a reduction might be accompanied by a slower propagation of the arterial pulse wave in the arm, the difference in time between the onset of the subclavian and radial pulses before and during the typical nitroglycerin action was determined in eleven experiments. In four of these the propagation of the pulse wave became somewhat slower, while in the remaining seven no definite alteration in the rate of propagation could be demonstrated. It seems evident, therefore, that the typical changes in the pulse may occur without a demonstrable alteration in the rate of pulse propagation from the neck to the wrist.

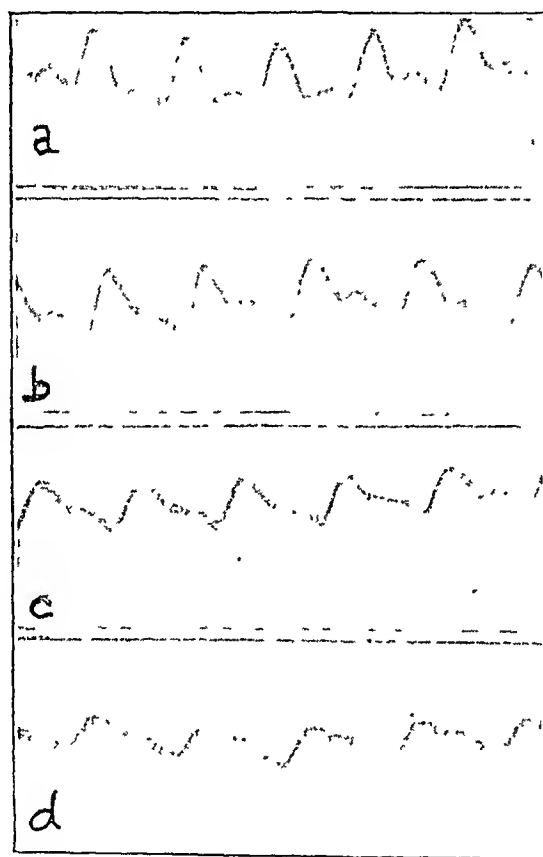
In a previous paper³ it was pointed out that the changes induced by nitroglycerin are more evident in the volume pulse of the arm than in the pulse recorded by placing a tambour over the carotid or sub-

3. Hewlett, A. W., van Zwaluwenburg, J. G., and Agnew, J. H.: The Pulse Flow in the Brachial Artery. II. Relation to the Average Blood Flow. Effect of Nitroglycerin. *THE ARCHIVES INT. MED.*, 1913, **12**, 13.

clavian arteries. Changes in the latter do occur, however, and subsequent records have shown that in some instances they are quite striking. One must therefore attribute the alteration in the arm pulse not only to local vascular changes, but also, in part, either to an alteration in the cardiac output or to changes in the vessels elsewhere in the body.

Electrocardiograms were made on several occasions before and during the nitroglycerin effect, but no noteworthy changes in form were noted.

Pituitary Extract.—It is well known that injections into animals of extracts prepared from the posterior lobe or from the pars intermedia



Curves showing alterations in the febrile pulse produced by the injection of 1.5 c.c. of pituitary extract (from Patient 2 (Sw.) of Table 1). *a.* Before the injection; *b.* seventeen minutes after the injection; *c.* twenty-two minutes after the injection; *d.* fifty minutes after the injection. Note that the volume pulse diminished in size and that its form changed from the pointed or collapsing type, often seen in fevers, to a sustained type.

of the pituitary gland, produce an arterial constriction with a rise of blood pressure. The effect of therapeutic doses on the blood pressure of certain patients was studied in this clinic by Dr. H. B. Schmidt, who found that while the systolic pressure was not altered in any constant manner, there was, as a rule, a moderate rise in the diastolic pressure.

TABLE 1.—EFFECT OF PITUITARY EXTRACT ON PULSE FORM IN PATIENTS SHOWING A POINTED TYPE OF PULSE

Case	Diagnosis	Time with Ref- erence to Pit. Extr.	Pulse Rate	Volume of Pulse Wave, c.c.	Blood Flow in Arm	Pointed Quality
1. S.	Tuberculosis	Before	118	0.8	++++
		Before	113	0.7	++++
		Before	109	0.8	++++
		Before	108	0.7	++++
		5 min. after	118	0.6	++++
		1.5 c.c.				
		10 min.	114	0.6	+++
		18 min.	107	0.6	+++
		30 min.	98	0.5	+
		38 min.	97	0.5	
2. S.	Tuberculosis	Before	108	0.33	++++
		Before	112	0.34	1.6	++++
		2 min. after	100	0.37	2.4	++++
		1.5 c.c.				
		4 min.	90	0.33	1.9	++
		6 min.	96	0.33	1.9	+++
		8 min.	104	0.33	1.7	+++
		13 min.	140	0.46	12.0	+++
		15 min.	111	0.30	4.3	+++
		17 min.	106	0.29	1.9	+
		22 min.	104	0.26	2.7	+
		25 min.	96	0.26	2.0	—
		35 min.	96	0.26	1.9	—
		40 min.	95	0.26	2.4	—
		50 min.	92	0.24	2.2	—
3. O. H.	Tuberculosis	Before	75	0.5	3.0	+++
		Before	80	0.5	2.5	+++
		3 min. after	73	0.45	2.6	+++
		1.5 c.c.				
		8 min.	74	0.45	2.5	+++
		10 min.	77	0.4	4.5	+++
		11 min.	73	0.45	4.5	++
		15 min.	76	0.45	2.0	++
		20 min.	80	0.45	2.4	+
		25 min.	80	0.4	2.8	+
		30 min.	82	0.4	+
		35 min.	75	0.35	2.4	—
		40 min.	74	0.3	+
		50 min.	75	0.3	1.2	—
		55 min.	70	0.3	2.0	—
4. C.	Fever	Before	117	0.5	4.0	+++
		Before	117	0.45	3.4	+++
		3 min. after		0.43	3.0	++
		1.5 c.c.	115			
		6 min.	115	0.35	3.0	+
		9 min.	117	0.4	5.0	—
		14 min.	119	0.4	6.0	—
		22 min.	112	0.4	—
		32 min.	120	0.35	6.7	—
5. K.	Fever	Before	65	0.5	++
		Before	66	0.5	++
		14 min. after	66	0.45	+
		1.5 c.c.				
		16 min.	64	0.4	+
		20 min.	70	0.35	—
6. H.	Tuberculosis	Before	98	0.6	7.5	+++
		Before	100	0.6	7.5	+++
		Before	102	0.6	6.5	+++
		3 min. after	100	0.6	6.8	++
		1.5 c.c.				
		7 min.	98	0.6	8.0	+++
		10 min.	97	0.6	8.0	++
		14 min.	102	0.6	9.0	++
		32 min.	103	0.5	7.3	++
		34 min.	104	0.6	9.0	++
		42 min.	97	0.5	7.2	++
		55 min.	100	0.5	7.0	++
7. A.	Tuberculosis	Before	122	0.4	2.0	+++
		Before	121	0.4	1.9	+++
		5 min. after	117	0.4	2.0	+++
		1 c.c.				
		10 min.	115	0.4	2.0	+++
		20 min.	117	0.4	2.4	+++
		30 min.	117	0.4	3.0	+++
8. L.	Aortic insuffi- ciency	Before	88	1.5	5.0	+++
		Before	94	1.4	+++
		5 min. after	84	1.3	++
		1 c.c.				
		7 min.	85	1.3	4.0	++
		10 min.	84	1.3	10.0	+
		17 min.	87	1.2	12.0	+
		22 min.	88	1.3	8.0	++

We have shown elsewhere⁴ that in many fevers, and particularly in typhoid fever and in febrile tuberculosis, the pulse form resembles that produced by nitroglycerin, but that its size is on the average smaller than normal. We have gained the impression, furthermore, that as the circulation shows evidence of failure during infections, the pulse becomes progressively smaller. The effect of pituitary extracts on this type of pulse was studied with the hope that some basis might be furnished for the use of such extracts during the circulatory failure which may complicate severe infections.

The effects that were observed after the intramuscular injection of pituitary extract⁵ are shown in Table 1 and in Figure 1. When striking changes occurred they consisted of: (1) a decrease in the size of the volume pulse; (2) a change from a pointed to a more sustained pulse, and (3) some tendency for a transient increase in the blood flow through the arm, which increase was not definitely related to the change in pulse form and volume. The alterations in pulse volume and form usually became evident in from five to ten minutes after the injection of the pituitary extract, and they persisted for thirty to fifty minutes or more. The onset and duration of this action on the pulse corresponds to the onset and duration of the effects on uterine contractions during labor, for Quigley⁶ asserts that these latter appear in three to ten minutes and last from sixty to ninety minutes.

In six of the eight observations here recorded the changes in the pulse produced by the pituitary extract were marked; in one they were indicated, while in one, in which 1 c.c. only was injected, they were absent. A considerable number of other pituitary extract injections were given without making a series of records. In some of these the above effects on the pulse were confirmed by a few records, while in still others the change to a smaller and more sustained radial pulse was noted on palpation of the radial artery. The carotid or subclavian pulse was recorded in a few instances and a similar tendency toward a more sustained form under the influence of pituitary substance was noted.

It seems certain, therefore, that pituitary extract in rather large doses produces a definite and fairly constant alteration in the size and form of the volume pulse recorded from the arm of febrile patients. This alteration is almost the opposite of that produced by nitroglycerin.

4. Hewlett, A. W.: The Pulse Flow in the Brachial Artery. IV. Reflections of the Primary Wave in Dicrotic and Monocrotic Pulse Forms, *THE ARCHIVES INT. MED.*, 1914, **15**, 609.

5. The preparation of Parke, Davis & Co. (pituitrin) was injected intramuscularly, usually in doses of 1.5 c.c.

6. Quigley, J. K.: Pituitrin in Obstetrics, *New York State Med. Jour.*, 1913, **13**, 317.

On account of this contrast, as well as on account of the known effect of pituitary extracts on animals, it seems highly probable that the changes observed in patients were due to arterial constriction. In our opinion, however, such a constriction is not likely to prove of great value in combating the circulatory failure during infections. In the first place, the volume pulse is usually quite small during such collapse, and pituitary extract, though restoring the normal form, makes the volume still smaller. In the second place, it seems probable that this type of circulatory failure is not due primarily to arterial relaxation, but to a deficient blood supply to the heart, owing perhaps to a stagnation of blood in the abdominal capillaries and veins. We have no evidence that pituitary extract will influence such a disturbance in the blood supply to the heart.

Veratrum Viride.—The effect of veratrum album on the pulse rate and the blood pressure of man has been recently studied by Collins,⁷ who found that large therapeutic doses reduce both the pulse rate and the blood pressure, and that these reductions may occur in certain cases without unpleasant gastro-intestinal symptoms. We have repeated these observations, using the hospital tincture or the fluid extract of veratrum viride, and were able to confirm Collins' observations. The effective dose, however, was considerably larger than that used by Collins, and it is evident that some method of standardization will be necessary if veratrum is to be employed in general practice.

Like Collins, we found that in some patients with chronic arterial hypertension, extraordinary reductions of the blood pressure can be produced by this drug. In one patient, for example, the systolic pressure fell from over 200 to 108 mm. in the course of a few hours. Other patients with normal as well as with increased blood pressure proved more resistant to the drug, and in one instance vomiting occurred at a time when no reduction of blood pressure had taken place. It is noteworthy, however, that the reduction in blood pressure may occur with none of the disagreeable symptoms which usually accompany a similar reduction after large doses of the nitrites. In several patients with chronic hypertension the tincture of veratrum viride was continued for several days in doses of 30 or more minims three or four times a day with no unpleasant symptoms, and with a slight but not very definite reduction in pressure.

In eight instances the pulse flow in the arm was recorded before and during the administration of veratrum viride. These records (Table 2) show that the fall in blood pressure produced by this drug is not accompanied by the changes in pulse size or form which char-

7. Collins, R. J.: The Clinical Actions of Veratrum, THE ARCHIVES INT. MED., 1915, 16, 54.

acterize the action of effective doses of nitroglycerin. It will be recalled that the latter cause an increase in the size of the volume pulse in the arm and that they tend to produce a pointed pulse. When veratrum viride is given in effective doses there may be a slight increase in the volume of the individual pulse waves, but this is not constant; nor is the form of the pulse wave materially altered. When changes in

TABLE 2.—EFFECTS OF VERATRUM VIRIDE

Case	Dose of Tincture, Minims	Blood Pressure	Pulse Rate	Volume of Pulse Wave, c.c.	Blood Flow in Arm	Pointed Quality
1. Kn.	Before	242-140	78	0.45	0.86	++
	After 90	210-122	60	0.52	1.0	+
2. Sm.	Before	166-106	92	0.42	1.7	—
	After 160	130-60	74	0.60	1.7	—
	Followed by Atropin 1/60 gr.	130-88	90	0.37	2.1	+
3. Sm.	Before	200-126	102	0.60	—
	After 120	122-70	70	0.58	Increased	—
4. Ja.	Before	112	0.76	++
	After	95	0.70	++
5. Ja.	Before	126-72	96	0.60	+
	After 140	126-70	96	0.78	+
6. McG.	Before	186-105	99	1.08	—
	After 200	183-110	100	1.2	++
7. In.	Before	260-132	84	+
	After	186-100	60	+
8. Ga.	Before	220-112	87	1.3	++
	After	204-103	60	1.3	Increased	—

TABLE 3.—EFFECT OF ATROPIN ON ARM PULSE*

No.	Time	Pulse Rate	Volume of Pulse Wave, c.c.	Blood Flow in Arm	Pointed Quality
1	After	66	0.4	4.0	—
	Before	73	0.3	3.5	+
2	Before	75	0.3	1.3	+
	After	85	0.3	1.7	++
3	Before	61	0.6	1.7	++
	After	82	0.5	3.4	++
4	Before	76	0.4	1.4	—
	After	80	0.5	2.0	—
5	Before	60	0.7	—
	After	62	0.6	Increased	—
6	Before	100	0.3	2.0	++
	After	140	0.4	3.8	++++

* Records taken before and about half an hour after the injection of 1/50 gr. atropin sulphate.

form did occur, the collapsing quality was more frequently lessened than increased. These slight alterations in the direction of a larger and more sustained pulse may in all probability be attributed to the slower pulse rate rather than to any change in the arteries.

Atropin.—On six occasions atropin sulphate was injected subcutaneously in doses of 1/50 grain, and the effect on the pulse flow was

recorded at the end of about half an hour. The subjects of these observations were normal so far as the cardiovascular apparatus was concerned. As may be seen from Table 3, the pulse rate was somewhat accelerated in four instances, considerably accelerated in one, and unaffected in one. The size of the volume pulse in the arm was not materially altered. The rate of blood flow was somewhat accelerated in five instances and diminished in one. The pulse form became slightly more pointed in four instances, and it is noteworthy that this change occurred in those cases which showed the more marked acceleration in the pulse rate.

Negative Results.—Records made after the injection of a number of other remedies which are believed to act on the cardiovascular apparatus showed no definite or marked effect on the pulse flow.

In seven patients the pulse flow was determined before and after the intravenous injection of strophanthin. In six patients who had a normal sinus rhythm, no striking changes were observed. Two of these had the typical pointed pulse of fever, while two others were suffering from mild grades of cardiac decompensation. The seventh patient, who showed auricular fibrillation and a rapid and irregular pulse, reacted with the usual slowing of the ventricular rate. This was accompanied by an increase in the size of the individual pulse waves.

Camphor dissolved in oil, in doses of from 5 to 10 grains, was injected subcutaneously into five patients, three of whom showed a pointed febrile pulse. No noteworthy alterations either in the pulse size or form were noted.

Pulse records were made in two patients who received subcutaneous injections of epinephrin solution for the relief of asthmatic attacks. One received 8 and the other 15 minims of Parke, Davis and Company's 1 to 1,000 solution. Although the paroxysms of asthma were relieved, no effect on the pulse form was observed.

Finally, a number of injections of strychnin sulphate were given in doses of $\frac{1}{20}$ to $\frac{1}{10}$ grain without any definite effect on the size or form of the pulse waves. In some of these cases, however, there appeared to be an increase in the rate of blood flow in the arm, which became most evident about half an hour after the injection.

CONCLUSIONS

Of the drugs studied, nitroglycerin, pituitary extract, veratrum viride, atropin, strophanthin, camphor, epinephrin and strychnin, only the first two produced definite and unmistakable alterations in the size and form of the volume pulse recorded from the arm of man. Nitro-

glycerin caused the pulse to become larger and more pointed, while pituitary extract had the opposite effect.

The fall of pressure produced by adequate doses of *veratrum viride* is not accompanied by definite changes in the pulse form. In this respect the action of this drug differs essentially from the action of nitroglycerin.

Lane Hospital.

STUDY OF A CASE OF DIABETES INSIPIDUS WITH SPECIAL REFERENCE TO THE MECHANISM OF THE DIURESIS AND OF THE ACTION OF PITUITARY EXTRACT ON IT*

C. D. CHRISTIE, M.D., AND G. N. STEWART, M.D.

CLEVELAND

The case of diabetes insipidus reported in this paper presented, on account of the high degree of the diuresis, an unusually good opportunity for the study of certain points in connection with the mechanism of the diuresis and the influence on it of extracts of the posterior lobe of the pituitary body. Although it was not possible to induce the patient to remain long enough in the hospital to enable us to complete our program, the results obtained seem worthy of being recorded.

The manner in which the excretion of water by the kidney is regulated has formed the subject of recent papers by Priestley¹ and by Haldane and Priestley.² They find, as T. M. Wilson,³ working under the direction of one of us, previously showed, that the drinking of water is followed by a small diminution of the specific conductivity of the blood serum. According to Wilson, the meaning of this would seem to be that "when the relative volume of serum is increased (e. g., by drinking water) the serum becomes more dilute as regards salts, and therefore has a diminished specific conductivity. When the serum diminishes in amount, water seems to pass out of it in greater proportion than salts." Haldane and Priestley were unable to demonstrate any change in the relative volume of the plasma which could be detected by estimating the percentage hemoglobin content.⁴ But Wilson, using a more delicate test, the determination of the relative volume of corpuscles and plasma by the electrical method,⁵ was able to show that coincident with the decrease in the conductivity of the serum there was a slight increase in its volume as compared with that of the corpuscles.

* Submitted for publication Feb. 15, 1917.

* From the Department of Medicine of Lakeside Hospital and the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

1. Priestley: *Jour. Physiol.*, 1916, 50, 304.

2. Haldane and Priestley: *Jour. Physiol.*, 1916, 50, 296.

3. Wilson, T. M.: *Am. Jour. Physiol.*, 1905, 13, 150.

4. Hemoglobin estimations and blood counts carried on throughout the period of observation on our patient failed to show any definite correspondence with the intake of water or the diuresis.

5. Stewart, G. N.: *Jour. Physiol.*, 1899, 24, 356.

It seemed to us not unlikely that during the great and abrupt changes in the diuresis produced in our case by posterior lobe extract, or by withholding water, or allowing it in the enormous amounts habitually taken by the patient, a greater and therefore more easily detectable effect might be produced on the blood than was possible in any normal individual.

An attempt was made by measuring the blood flow through the hands to determine whether posterior lobe extract produced any effect on the superficial vessels which might afford support to the view that it affects the diuresis by a change of caliber of the renal vessels.

The ability of the kidney to excrete a concentrated urine, and its behavior to so-called "functional tests," were also investigated.

An attempt to review the theories which have at various times been held in regard to the mechanism of diabetes insipidus would be out of place. It will suffice for our purpose to refer to a few of the investigations which have seemed to connect the condition with a change in the activity of the pituitary body.

The frequent association of diabetes insipidus with tumors and injuries about the base of the brain, and the demonstration by Claude Bernard that puncture of the floor of the fourth ventricle occasionally produced a polyuria without glycosuria, led many observers to the belief that the disease was in some way dependent on the central nervous system. Magnus and Schäfer⁶ demonstrated that extracts of the hypophysis caused an increased urine output. Schäfer and Herring⁷ showed the diuretic effect of hypophyseal extract to be a property of the pars intermedia. They claimed the diuretic action was due to a direct stimulation of the kidney cells, associated with local dilatation of the kidney vessels. The work of Schäfer and Herring has been pretty generally accepted. These observations suggested that diabetes insipidus might be a manifestation of a hyperactive pituitary body.

Cushing⁸ later pointed out that patients and animals frequently developed a diuresis following the removal of the posterior lobe of the pituitary body which was not unlike diabetes insipidus. Frank⁹ observed a patient in whom diabetes insipidus had developed coincidently with the lodgment in the sella turcica of a bullet which encroached on the posterior lobe of the pituitary body. Lewis and Mathews¹⁰ produced an analogous condition in dogs by inserting foreign material in the sella which encroached on the pituitary body. Such observations cast doubt on the conception that diabetes insipidus was the result of an overfunctioning posterior lobe. Cushing,⁸ von den Velden and Farmi¹¹ expressed the view that diabetes insipidus was the result of an underfunctioning pituitary body.

There are in the literature a number of instances of patients suffering from diabetes insipidus who have experienced amelioration in the symptoms after intramuscular injection of posterior lobe extract. Recently recorded instances

6. Magnus and Schäfer: *Jour. Physiol.*, 1901-1902, **27**, 9 (*Proc. Physiol. Soc.*).

7. Schäfer and Herring: *Phil. Tr. Roy. Soc.*, 1906, **199**, B. p. 1.

8. Cushing: *The Pituitary Body and Its Disorders*, 1912.

9. Frank: *Berl. klin. Wchnschr.*, 1912, **49**, 393.

10. Lewis and Mathews: *THE ARCHIVES INT. MED.*, 1915, **15**, 451.

11. Von den Velden and Farmi: *Berl. klin. Wchnschr.*, 1913, **50**, 2083.

are those of Motzfeldt¹² and Eisner.¹³ Motzfeldt reported three cases in which the urine output was cut down markedly, and in one of the patients there had been almost complete relief from the symptoms by the administration of the fresh posterior portion of the gland by mouth.

REPORT OF CASE

History.—C. F., woman, single, aged 31, was admitted to the Lakeside Hospital medical service, Nov. 13, 1916.

The patient's health had always been good until the present trouble began. There was no history of acquired or congenital syphilis. She was well and working regularly four years prior to admission, when she noticed rather suddenly that she was passing larger quantities of urine than usual and that her thirst was unquenchable. She was forced to give up her work within a short time. She gradually became very weak, but did not lose weight. Since that time her condition has remained much the same. Some days the urine output and the thirst have been greater than on other days. The urine output, as near as we could determine from the history, has ranged from 8 to 16 liters daily. During this time she has had several attacks in which she would be confined to bed with shortness of breath and swollen legs. She has also suffered intensely with a "breaking out" on the hands and arms, worse in winter, when the pain and itching are almost intolerable.

Physical Examination.—If it were not for an anemia the patient would appear in robust health. She is well developed and slightly inclined toward adiposity. The skin was extremely dry and showed a high grade of anemia. On the dorsum of the forearms and hands there was a papulosquamous eruption. The skin in these areas was extremely rough and dry, with multiple fissures. There was some slight oozing in spots, with scab formation (dermatitis hiemalis). The examination of the eyes, pupils and eyegrounds was entirely negative. There was a venous hum; no thyroid enlargement. The examination of the chest was negative, aside from rather extreme cardiac enlargement. No murmurs or adventitious sounds were heard over the precordium. The pulse was regular and there was no elevation of blood pressure. There was a moderate increase in the volume of the liver, but it was not tender. Examination of the nervous system revealed no abnormal findings.

The urine was pale, of large quantity, and low specific gravity. There was a faint trace of albumin in the admission specimen, but subsequent examinations revealed none. There were no casts.

The blood showed: hemoglobin (Sahli), 35 per cent.; white blood cells, 7,800; red blood cells, 3,700,000.

Lumbar puncture revealed no increase in pressure; fluid normal in appearance; two cells per cubic centimeter. The Noguchi and Wassermann tests were negative.

Roentgenograms of the region about the sella turcica showed no increase in the size.

One sugar determination was made on the blood of this patient by the method of Lewis and Benedict. It was found to be 0.168 gm. per hundred c.c. This would represent a distinct hyperglycemia, but the patient had never shown sugar in the urine, so immediately following the above determination she was given 250 gm. of dextrose by mouth and subsequent urine specimens were examined for sugar. They were all negative. The reduction in the blood was probably not due to sugar.

12. Motzfeldt: Boston Med. and Surg. Jour., 1916, **174**, 644.

13. Eisner: Deutsch. Arch. f. klin. Med., 1916, **120**, 438.

METHODS OF STUDY

Considerable difficulty was encountered in the management of this case. The patient frequently drank 2 liters of water at a time and voided a similar amount of urine. Strict supervision was required. She was placed in a room by herself and was constantly watched by a nurse. Four nurses were engaged in her care. Water was measured into flasks in the laboratory and delivered to the room as they were needed. Other fluids were measured and figured in with the intake. Food was given to the patient at 8 a. m., 12 m., and 5 p. m., no food being allowed between meals. The diet was general except on days indicated in Figure 1 on which water was restricted. On these days the regular Mosenthal renal test diet was given. The days when the renal test diet was being taken, 1,000 c.c. of water was given with each meal instead of the stipulated amount. No water was allowed between meals and no particular attempt was made to limit the water after 8 p. m. on these days. The weight was obtained at 8 a. m. without permitting the patient to drink or to void after 7 a. m.

Blood specimens were always taken from the median cephalic vein into a small amount of oxalate, for blood ureas, sugar, etc. For hematocrit and electrical conductivity measurements, it was taken into a flask with beads and immediately defibrinated.

EFFECT OF POSTERIOR LOBE EXTRACT

The profound effect of intramuscular injection of a commercial extract of a pituitary solution of the posterior lobe of the pituitary body on the water intake and the urine output is clearly brought out in Figure 1. As nearly as could be determined, the effect was evident in about one hour following the administration. For the first three days no posterior lobe extract was administered. On the first day it will be noticed there was considerable disparity between the intake and output. This was undoubtedly due to an error in counting the flasks on the part of attendants, who were not accustomed to the routine, as the weight remained constant. On the following day the water intake was restricted for twenty-four hours, but the patient excreted about 5,400 c.c. more urine in this day than she took fluids. Figure 2 shows that on this second day the patient lost $11\frac{1}{2}$ pounds in weight. This loss is accounted for by the excess urine output over the water intake. On the following day, December 5, the patient kept some of the ingested fluid and recovered some of her admission weight. On the three following days, December 6 to 8, the patient was given posterior lobe extract, 1 c.c., three times daily, intramuscularly. Although she was allowed water at discretion, the tremendous drop in water intake and urine output will be noted. Her thirst was greatly diminished and the weight remained practically constant for the three days. December 8, or the third day of the posterior lobe extract period the fluids were again restricted to a much greater degree than on December 4, but on the 4th she passed a great excess of urine over the intake and was very uncomfortable, while on the 8th under posterior lobe extract the output was only slightly in excess of the intake, the

weight fell about 3 pounds and the patient suffered only moderate discomfort from thirst. From December 9 to 11, inclusive, no posterior lobe extract was given and no fluid restriction imposed. The output and intake reached a higher figure than we have ever seen recorded. On each of the following three days, or from the 12th to the 14th, inclusive, the patient was given 1 c.c. of posterior lobe extract, and it will be noticed that the intake and the output were about one-third of what they were when she received 3 c.c. daily. The weight gradually crept up on these three days to near her admission weight. December 15 the fluids were again restricted and the patient given 3 c.c. of posterior lobe extract. From 5 p.m. until the following morning, December 16, at 10 a. m., restriction of water was made as severe as

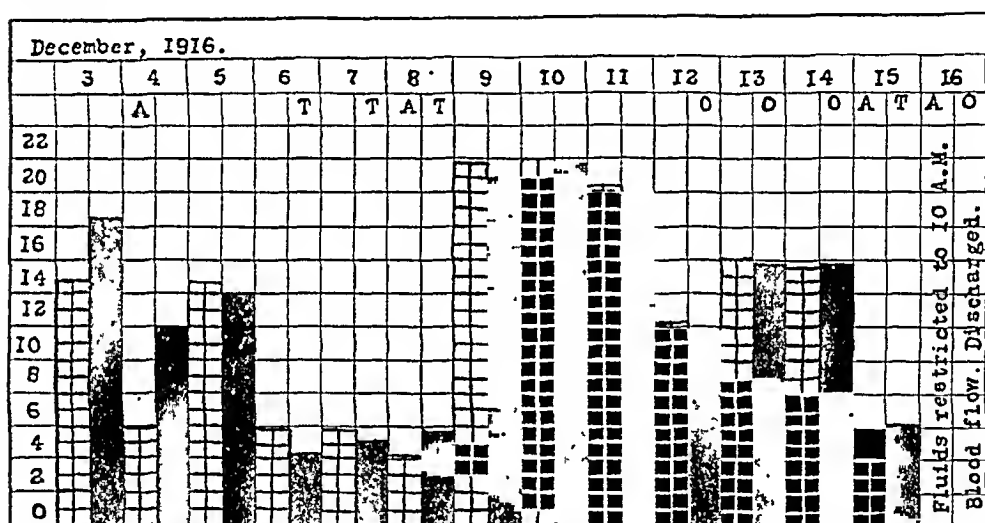


Fig. 1.—Quantity of intake and output per day expressed in liters. Hatched column, intake; solid column, output. On days marked with an A, fluids were restricted; other days there was no fluid restriction. Days indicated by a T, posterior lobe extract was given in 1 c.c. dose, intramuscularly, three times daily. Days marked with an O, a single dose of posterior lobe extract was given intramuscularly.

possible to see whether any effect could be produced on the conductivity of the serum and its relative volume. The patient in the twenty-six hours ending at 10 a. m., December 16, lost 6 pounds in weight.

While the antidiuretic effect of posterior lobe extract given intramuscularly was extremely evident, we were not able to show that the drug prepared for oral administration exerted the same beneficial results, although the results have not been completely negative. Our experience with the oral administration of fresh posterior lobes from cattle has been so far about the same as with the oral administration of the prepared extract. Of course, it is obviously impossible to continue the injections, for it would require at least three a day to keep

the patient in comfort, as the effect lasts only from five to seven hours. After that time there is complete escape from the effect. Larger doses, 2 c.c. per injection, were no more satisfactory; in fact, less so, for the effect did not last any longer and there were more unpleasant accessory actions, as increased irritability of the bladder, with frequent desire to urinate.

As regards the effect of the drug on the blood pressure, the systolic pressure was never found above 130 mm. of mercury, and the diastolic ranged near 75 mm. Although this patient had a hypertrophied heart with dilatation, we felt there was no contraindication to continuing the injections. No change was noted in the blood pressure following the administration.

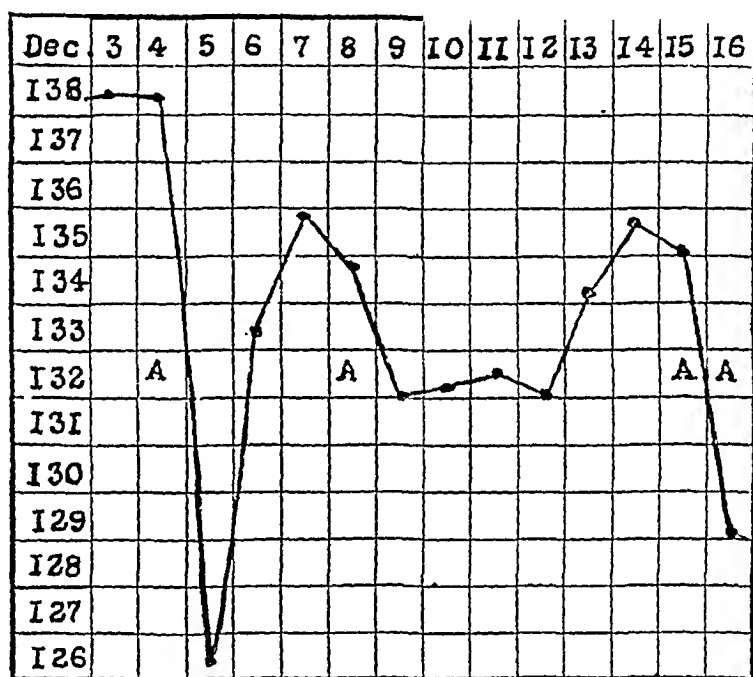


Fig. 2.—Represents the weight of the patient expressed in pounds. These weights were obtained at 8 a. m. On days marked with an A, fluids were restricted.

CONDUCTIVITY AND RELATIVE VOLUME OF SERUM

Table 1 shows the results of observations on three specimens of blood and serum. Although the number of specimens was not as great as could have been wished, owing to the reluctance of the patient, the results seem to show clearly enough a definite although slight increase in the conductivity of the serum and a correspondingly slight decrease in its volume relatively to that of the corpuscles when the intake of water was greatly diminished, either by actual restriction or by giving posterior lobe extract, which lessened the thirst. December 11, as will be seen from Figure 1, the patient took in and excreted over 20 liters

of water. December 15, under posterior lobe extract and slight water restriction (Table 6), the intake was only 4 liters and the excretion by the kidney $6\frac{1}{2}$ liters.

In the seventeen hours preceding the collection of the blood specimen, December 16, water was restricted as much as possible (little more than 1 liter). It will be seen (Table 1) that the conductivity of the serum of December 16 is the highest, and its relative volume the lowest of the three specimens, while the corresponding numbers for December 16. The relative volume of the serum was determined both by the electrical method and the hematocrit. While the hematocrit only gives relative results on account of the difficulty of reaching an absolutely constant end-point, the fact that the longer the centrifugalization is continued the nearer do its readings come to those of the electrical method, confirms the accuracy, at least for comparative purposes, of the results.

TABLE 1.—SHOWING CONDUCTIVITY AND RELATIVE VOLUME OF BLOOD SERUM

Date	K $\times 10^4$ at 5 C.		Percentage Volume of Serum by	
	Blood	Serum	Electrical Method	Hematocrit*
12/11	54.6	78.6	82.9	79 (6½ min.) 80 (13½ min.)
12/15	52.4	79.5	80.2	76.5 (7 min.) 77.5 (12 min.) 78 (17 min.)
12/16	53.7	82.5	79.0	73 (14 min.) 74.8 (21 min.) 75.7 (21 min.) 76.5 (36 min.)

* Turned at rate of 4,000 revolutions per minute.

The differences in conductivity do not seem to be even as great as those observed by Wilson and by Haldane and Priestley, in whose observations the variations in the quantity of water transported by the blood were much smaller. It must be remembered that the blood is simply the transportation system for the water, and the amount in transit at any moment is no more an index of the amount transported per hour or day than the number of cars of wheat on a railway on a given day are an index to the size of the wheat crop. While it would not be justifiable from so small a number of observations to draw the conclusion that the kidney is stimulated to increase its excretion of water by an even smaller excess of water in the blood in diabetes insipidus than in health, the suggestion may be made that if the kidney is really abnormally sensitive to water excess, so that the threshold of the stimulus is lowered, it would afford an explanation of the condition. It must be remembered, however, that in this patient the pro-

portion of plasma in the blood is greater than normal, so that, on the assumption that the total volume of blood is not less than normal, the addition of a given amount of water to the blood would not dilute the plasma so much or increase its relative volume so much as in a normal person.

MEASUREMENT OF THE BLOOD FLOW IN THE HANDS

This was done on four days by the method previously described by one of us.¹⁴ The idea was to see whether posterior lobe extract caused any definite effect on the blood flow through the superficial vessels at the time when it was causing a decrease in the diuresis. If its anti-diuretic effect was associated with an alteration in the flow through the superficial vessels (not associated with a change in the heart's action, which there was no reason to suspect), it was argued that this would render it more probable that vascular reactions were occurring elsewhere, as in the kidney, which might account for the diminution in the excretion of the urine. A dilatation in peripheral areas might very well be associated with a renal constriction. Unfortunately, the existing dermatitis on the patient's hands rendered them peculiarly susceptible to contact with water, so that the uniformity of results in the control observations was less than is usually seen under hospital conditions. She said the water increased the irritation, and she had a similar objection to protecting the skin by oil or vaselin, so that it proved impossible to get as many observations as we desired. The skin affection and the anemia, which is always associated with subnormal hand flow, rendered the exposed parts abnormally susceptible to changes of temperature in the wards. In spite of these drawbacks, however, the four experiments carried out, the condensed results of which are given in Table 2, do seem to indicate an increase in the hand flow under the influence of posterior pituitary lobe extract.

The highest flows were seen on December 15, when the antidiuretic effect was well established. Not only was the flow decidedly better than in the two control experiments (on December 11 and December 14) when no posterior lobe extract was being given, but the flow was steady practically from the time the hands were put into the calorimeter, and did not slowly creep up over a considerable period of time, as in the control experiments. This slow, almost reluctant, increase is a feature of the flow in the hand when its vessels have an abnormally great tendency to vasoconstriction, and when the maximum flow is reached it will then, in any case, be small. Both criteria, therefore, indicate that on December 15 the posterior lobe extract had to a considerable extent overcome the tendency to cutaneous vasoconstriction. The measurement of December 16, although it gave a somewhat lower flow than

14. Stewart, G. N.: *Heart*. 1911. 3, 33.

the first control measurement (of December 11), is not really out of harmony with this. The patient had received no posterior lobe extract for seventeen hours, but one hour before the measurement was started she was given 1 c.c. Also she had lost six pounds in weight during the previous period of water restriction, and much of the water she was now taking was not being excreted by the kidneys, but was going back into the tissues. Furthermore, she had been sitting around the ward, as she wanted to leave the hospital, and said that she had been cold all the morning. Her hands were cold when they were put into the bath. The patient said she had noticed that after receiving the injections the skin of the hands, which was habitually dry, became more moist and that her hands, which were habitually cold, became warmer. We confirmed the statement that sweat appeared distinctly on the hands when she was under the influence of posterior lobe extract, while at other times they were extremely dry.

TABLE 2.—BLOOD FLOW IN THE HANDS—

Date	Pulse Rate	Temperature (C.) of				Volume of Hands in C.c.		Heat Given Off in Grams, Calories		
		Room	Arterial Blood	Calorimeters		Right	Left	Right	Left	In Min.
				Right	Left					
12/11/16	78	24.0	36.92	31.81	31.75	347	360	573	761	10
		24.0		31.88	31.86			725	1,032	10
12/14/16	75	24.4	36.58	31.75	31.72	357	362	237	270	10
		23.4						348	315	10
12/15/16	74	24.0	36.10	32.03	32.07	366	358	933	1,108	10
		24.5		32.17	32.16			930	1,092	10
12/16/16	78	24.2	36.90	31.30	31.35	357	358	602	754	10
		24.8		31.35	31.45			652	855	10

The dermatitis was worse on the left hand and arm, which probably accounts for the greater flow in that hand on December 11, 15, and 16. That the inequality was due to a vasomotor and not to a mechanical difference is shown clearly in the experiment of December 14, when, under the influence of markedly increased vasoconstriction due to cold (two of the fingers on the right hand had been "dead" earlier in the day, she said), the inequality disappeared. If the flow for the second and third ten-minute periods of the experiment be added, they are practically equal for the two hands.

ABILITY OF THE KIDNEY TO CONCENTRATE THE URINE

Erich Meyer¹⁵ advanced the hypothesis that the diuresis of diabetes insipidus is primarily the result of a disease of the kidney. Such a

15. Meyer, Erich: *Deutsch. Arch. f. klin. Med.*, 1905, **83**, 1; *Ztschr. f. klin. Med.*, 1912, **74**, 352.

view has been maintained essentially on the assumption that the kidneys of patients afflicted with diabetes insipidus were not able to elevate the concentration of the urine. Mosenthal¹⁶ has recently offered evidence in favor of Meyer's hypothesis. Histologic examination of the kidneys in diabetes insipidus lends no support to the view that the condition is due to any structural alterations in these organs.

There are now quite a few instances recorded in the literature of patients afflicted with diabetes insipidus whose kidneys have shown definite concentrating ability. Fitz,¹⁷ in this country, has reported a case in which he was able to demonstrate a moderate ability on the part of the kidney to elevate the specific gravity of the urine. Both Motzfeld¹² and Eisner,¹³ by the use of pituitary extract injections, were able to show the same thing, only to a more marked degree.

Our patient had a severe anemia, which in itself is sufficient to impair the ability of the kidneys to concentrate the urine, as has been

—OF A PATIENT WITH DIABETES INSIPIDUS

Blood Flow in Gm. per Minute		Flow per 100 C.c. of Hand per Minute		Period in Calorimeter	Remarks
Right	Left	Right	Left		
12.46	16.35	3.59	4.54	First ten minutes	No posterior lobe extract
15.98	22.66	4.60	6.29	Second ten minutes	
5.45	6.17	1.52	1.70	Second ten minutes	No posterior lobe extract
7.94	7.14	2.22	1.97	Third ten minutes	
21.29	25.49	5.81	7.12	First ten minutes	Posterior lobe extract action
21.84	26.15	5.96	7.30	Second ten minutes	
11.94	15.09	3.34	4.21	Second ten minutes	Doubtful posterior lobe extract action
13.05	17.43	3.65	4.86	Third ten minutes	

recently shown by Mosenthal,¹⁶ Christian¹⁸ and unpublished data accumulated by one of us (C). Probably if it had not been for this disturbing element our results would have been more striking than they are.

In studying the concentrating ability of the kidneys the patient was put on a standard Mosenthal renal test diet. This diet contains 13.4 gm. of nitrogen, 8.5 gm. of sodium chlorid and 1,760 c.c. of fluids. No alterations were made in the procedure except to elevate the quantity of water served at each meal. Days when these test diets were run have been indicated in Figure 1 by the term "water restriction." On all of the days when the patient was taking the renal test diet no attempt was made to restrict the patient's water intake after

16. Mosenthal: THE ARCHIVES INT. MED., 1915, **16**, 733.

17. Fitz: THE ARCHIVES INT. MED., 1914, **14**, 706.

18. Christian: THE ARCHIVES INT. MED., 1916, **18**, 429.

8 p. m. So in reality we only made twelve-hour observations; but for completeness the "night" urine was balanced for estimating total nitrogen and chlorid output.

Table 3 shows the response of the patient's kidneys to a renal test meal on November 27, six days before our more accurately controlled period began. No posterior lobe extract was given. The diuresis was not so great on this day as it had been on other days, and the specific gravity of the night urine was distinctly higher than usual. The excretion of nitrogen and salt was perfectly normal. Although there was moderate fixation of the specific gravity, the percentage excretion of salt and nitrogen would indicate definite concentrating ability on the part of the kidney.

TABLE 3.—RESPONSE OF PATIENT'S KIDNEYS TO A RENAL TEST MEAL WITHOUT POSTERIOR LOBE EXTRACT

Time	Amount, C.c.	Sp. Gr	Chlorids	Per Cent.	Nitrogen	Per Cent.
8 to 10	1,226	1.000				
10 to 12	955	1.000				
12 to 2	1,150	1.004				
2 to 4	750	1.003				
4 to 6	400	1.005				
6 to 8	615	1.003				
Total day..	5,096	4.59	0.09	5.79	0.11
Night, 8 to 8	1,315	1.007	3.29	0.24	5.67	0.43
Total output.....	6,411	7.88	11.46	
Intake.....	6,510	8.5	13.4	
Balance.....	+399	+0.62	+1.94	

It was thought that if extreme water restriction were imposed with the patient under the régime of a renal test meal and no posterior lobe extract, that the concentrating ability of the kidney might be made more evident than in Table 3. Table 4 shows the result of such an observation on December 4. This was the second day of the observation period and during the first ten hours the patient was restricted to 1,760 c.c. of water. It was necessary to terminate the observation at 6 p. m., and allow water. It will be seen that the patient excreted 5,400 c.c. more fluid than she took in and lost 11½ pounds in weight, as shown in Figure 2, on December 5. The nitrogen and salt were not determined in this instance, but it will be noticed that the concentrating ability of the kidney was only slightly in evidence.

TABLE 4.—URINE CONCENTRATION UNDER EXTREME WATER RESTRICTION WITHOUT POSTERIOR LOBE EXTRACT

Time	Amount, C.c.	Specific Gravity
8 to 10.....	1,885	1.003
10 to 12.....	722	1.002
12 to 2.....	1,270	1.005
2 to 4.....	1,075	1.007
4 to 6.....	910	1.007
Total day.....	6,062	
Night, 6 to 8.....	5,600	1.002
Total output.....	11,562	
Intake.....	6,160	
Balance.....	-5,402	

TABLE 5.—SHOWING RESPONSE OF PATIENT'S KIDNEYS TO A RENAL TEST MEAL

Time	Amount, C.c.	Sp. Gr.	Chlorids	Per Cent.	Nitrogen	Per Cent.
8 to 10.....	320	1.001*				
10 to 12.....	100	1.011				
12 to 2.....	100	1.013				
2 to 4.....	155	1.010				
4 to 6.....	135	1.015				
6 to 8.....	207	1.006				
Total day.....	1,017	2.01	0.2	3.27	0.3
Night, 8 to 2.....	4,370	3.49	0.08	5.87	0.13
Total output.....	5,387	5.50	9.04	
Intake.....	4,210	4.40	12.60	
Balance.....	-1,177	-1.10	+3.54	

* 1 c.c. posterior lobe extract 9 a. m., 3 p. m. and 9 p. m.

Table 5 represents the response of the patient's kidneys to a renal test meal given December 8 of our period of observation. The patient, as shown in the table, received three intramuscular injections of posterior lobe extract of 1 c.c. each, at 9 a. m., 3 p. m. and 9 p. m. In this experiment, as well as in the subsequent one, it will be noticed that

the 9 a. m. dose of posterior lobe extract did not show any marked effect until after 10 a. m. It will be seen, however, that there is a distinct ability on the part of this patient's kidneys to elevate the specific gravity of the urine. The nitrogen and salt elimination appear normal. There seems to be a tendency, however, for the solids to be excreted in greater quantities during the night. But this was just as apparent when the patient was not under the influence of the drug. The effect of the dose given at 9 p. m. usually wore off between 2 and 4 a. m.

Table 6 shows the results of a test diet day on December 15 of our period of observation. The results confirm those shown in Table 5, although the patient did not seem to get so much under the effect of the three doses of posterior lobe extract as she did in that instance.

TABLE 6—RESULTS ON URINE OF A TEST DIET

Time	Amount, C.c.	Sp. Gr.	Chlorids	Per Cent.	Nitrogen	Per Cent
8 to 10 ..	1,010	1.001*				
10 to 12 ..	230	1.012				
12 to 2 ..	922	1.004				
2 to 4 .	360	1.007				
4 to 6 ..	162	1.012				
6 to 8 .	124	1.007				
Total day...	2,808	..	4.40	0.15	3.75	0.13
Night, 8 to 8	3,710	1.001	4.04	0.11	5.35	0.14
Total output	6,518	8.44	9.10	
Intake ...	4,010	4.25	11.88	
Balance ..	-2,508	...	-4.19	+2.78	

* 1 c.c. posterior lobe extract 9 a. m., 3 p. m. and 9 p. m.

There was a phenolsulphonephthalein excretion of 70 per cent. in two hours. Blood urea was twice estimated. Two hours after an essentially carbohydrate breakfast it was 0.017 gm. per 100 c.c. The urea index at the same time was 157. Another blood urea estimation two hours following a protein meal gave 0.028 gm. per 100 c.c. and a urea index of 81.

We can conclude, then, that with posterior lobe injections this patient's kidneys had ample ability to concentrate the urine. Without the drug there was evidence that the kidneys had only a meager ability to elevate the specific gravity. Other functional tests all indicated a normal kidney excretion.

SUMMARY

The regulation of the excretion of water by the kidney was studied in a case of diabetes insipidus. It was supposed that on account of the high degree of the diuresis, the great quantity of water ingested and transported, and the marked diminution in the excretion and ingestion caused by pituitary posterior lobe extract, the conditions for such a study would be unusually favorable.

The conductivity of the blood serum was slightly increased and the relative volume of serum slightly diminished when the water excretion was lessened by posterior lobe extract or by water restriction.

The blood flow in the hands seemed to be increased during the antidiuretic action of posterior lobe extract. This, so far as it goes, supports the view that a vascular effect in the opposite direction on the renal vessels may be responsible for the diminution in the urine excretion.

It was shown that under the action of posterior lobe extract the kidneys had the power of effecting a considerable concentration of the urine. Other kidney functional tests gave a normal response. Accordingly, no indication was obtained that the condition was in any way associated with a pathologic alteration in the kidney.

MULTIPLE HEMANGIOMAS OF THE SKIN ASSOCIATED WITH DYSPITUITARISM *

GEORGE DOUGLAS HEAD, B.S., M.D.

MINNEAPOLIS

Scattering angiomas (telangiectases) of the skin are frequently found in apparently normal persons and have no pathologic significance. On the other hand, they may develop in large numbers and in varying sizes on the skin of persons with diseases of the liver (cirrhosis and cancer), in chronic jaundice from gallstones, or simple catarrhal jaundice, also in tertiary lues (S. Ehrmann,¹ Trawinski²), and as a result of Roentgen-ray skin exposure (Kingsbury³).

A family form of multiple telangiectases of the skin and mucous membranes, with recurring epistaxis, has been described by Osler,⁴ and later by Hanes⁵ and Langmead.⁶

In this group of cases the dilated capillaries are confined largely to the mucous membranes of the mouth and nose and the skin of the face. The tendency to recurring nasal hemorrhages is a prominent feature and there is an hereditary history of recurring hemorrhages in the family.

An exceedingly rare form of generalized telangiectases (telangiectases circumscripta universalis) involving the skin of the trunk, the arms and legs has also been recognized by Brocq⁷ and Vidal⁸ (quoted by Osler) and by Osler⁹ himself.

In this condition the spots are not raised above the surface of the skin. They vary in size from 2 to 6 mm. in diameter and often coalesce in large blotches. No individual blood vessels are seen, and the condition is confined to the capillaries.

A case of multiple telangiectases of the face, mouth, lips, cheeks, sides of neck and upper chest, without hemorrhages and with enlargement of the right lobe of the thyroid gland, has been recorded by Adamson.¹⁰

* Submitted for publication March 12, 1917.

1. Wien. med. Wchnschr., 1907, No. 16, p. 778.

2. Monatsh. f. prakt. Dermat., 1910, 1, 45.

3. Jour. Cutan and Genito-Urin. Dis., 29, 242.

4. Bull. Johns Hopkins Hosp., 12, 333.

5. Bull. Johns Hopkins Hosp., 20, 63.

6. Proc. Roy. Soc. Med., 3, No. 5.

7. La pratique dermatologie. 4.

8. Bull. et mém. Soc. méd. d. hôp. de Paris, 1880-1881, p. 186.

9. Bull. Johns Hopkins Hosp., 18, 401.

10. Proc. Roy. Soc. Med., 2, Part 1. p. 128.

Angiomas of the skin associated with clinical manifestations of pituitary gland changes do not seem to have been observed. Pierre Marie,¹¹ in Case 2 of his original description of acromegaly, speaks as follows relative to the vascular changes:

With regard to the circulation and blood vessels, there is one thing to note, the tendency to varicose veins which existed in Case 2. In this patient, in fact, there were not only distinct venous dilatations, with varices, but also large hemorrhoids, which caused much suffering and very abundant loss of blood.

Cushing,¹² while describing peculiar boggy recurring edemas of the skin on the face, over the face and in the submental regions of a number of second series of dogs, mentioned no changes in the vessels of the skin, nor is reference to be found of angiomas of the skin in any of the clinical cases reported in his monograph.

Dunn,¹³ in reporting a case of acromegaly, mentions "distention of the supra-orbital veins," but states that this distention became evident on exertion or excitement. No reference is made to telangiectases on the skin, mucous membranes or elsewhere on the body.

The two cases here reported are remarkable examples of multiple hemangiomas of the skin associated with clinical manifestations of pituitary gland changes. In Case 1, the skin of the scrotum, penis, inside of the thighs, arms, back and abdomen was affected. In Case 2 the skin of the scrotum and the mucous membranes of the lips and mouth were involved. The case reports are as follows:

REPORT OF CASES

CASE 1.—*History*.—Carl L., aged 28, Swedish, single, farmer, was admitted to the University Hospital, Oct. 27, 1913, complaining of pains in the hands, feet and head.

The patient's family history was unimportant, except that his mother had died of apoplexy. Four brothers and three sisters were living. The patient denied venereal disease. He used tobacco and drank moderately of beer and whisky.

At 8 years of age he had influenza, and measles at 12 years. When about 10 years of age he developed a left-sided inguinal hernia which still persisted. There was no history of nosebleed.

The present symptoms of which he complained date back to his childhood. When about 8 years of age he was taken sick with some kind of illness associated with fever, which was called "la grippe." Following this sickness, of which he could give no accurate account, he began to have severe pains in his hands and feet. The pains were not severe enough to call a physician. He remembered that some swelling occurred in the hands and feet along with the pains. After recovery from this illness he was fairly well until about one year later, when he was in bed for six weeks with fever, and pain and swelling in the hands and feet. The pain was confined to the smaller joints.

12. *The Pituitary Body and Its Disorders*, Philadelphia, 1912, p. 19.

11. *Tr. New Sydenham Soc.*, London, 1891, p. 12.

13. *Am. Jour. Med. Sc.*, 148, 127.

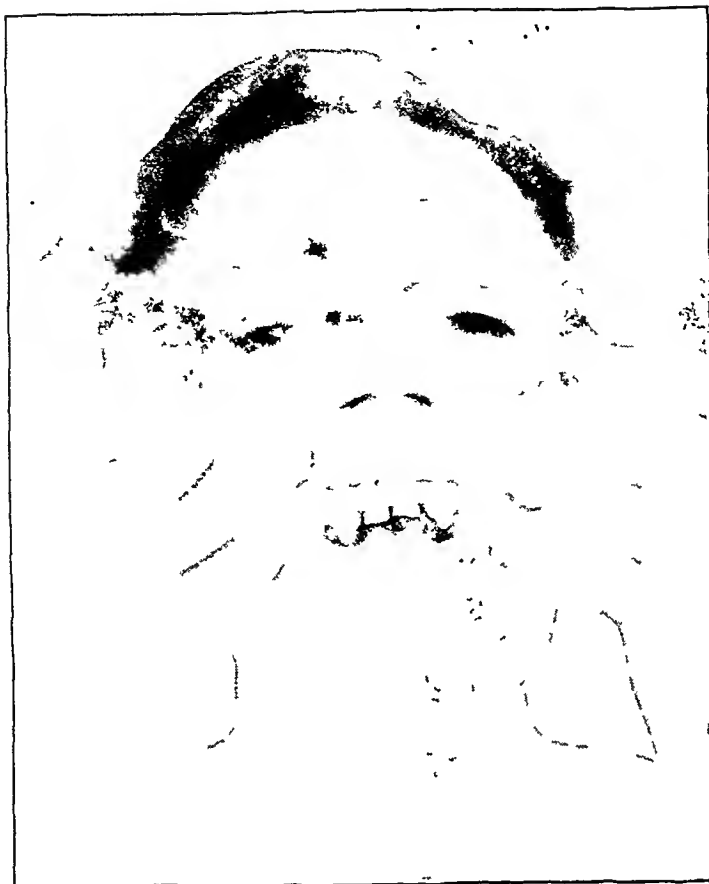


Fig. 4.—Patient, Case 1, showing spacing of teeth.



Fig. 5.—Patient, Case 1, showing telangiectases and hemangiomas of scrotum. The elbows and scrotum were coming all the same on without any burn-
stanes of lips, inside of and any relationship between
ains in the limbs.

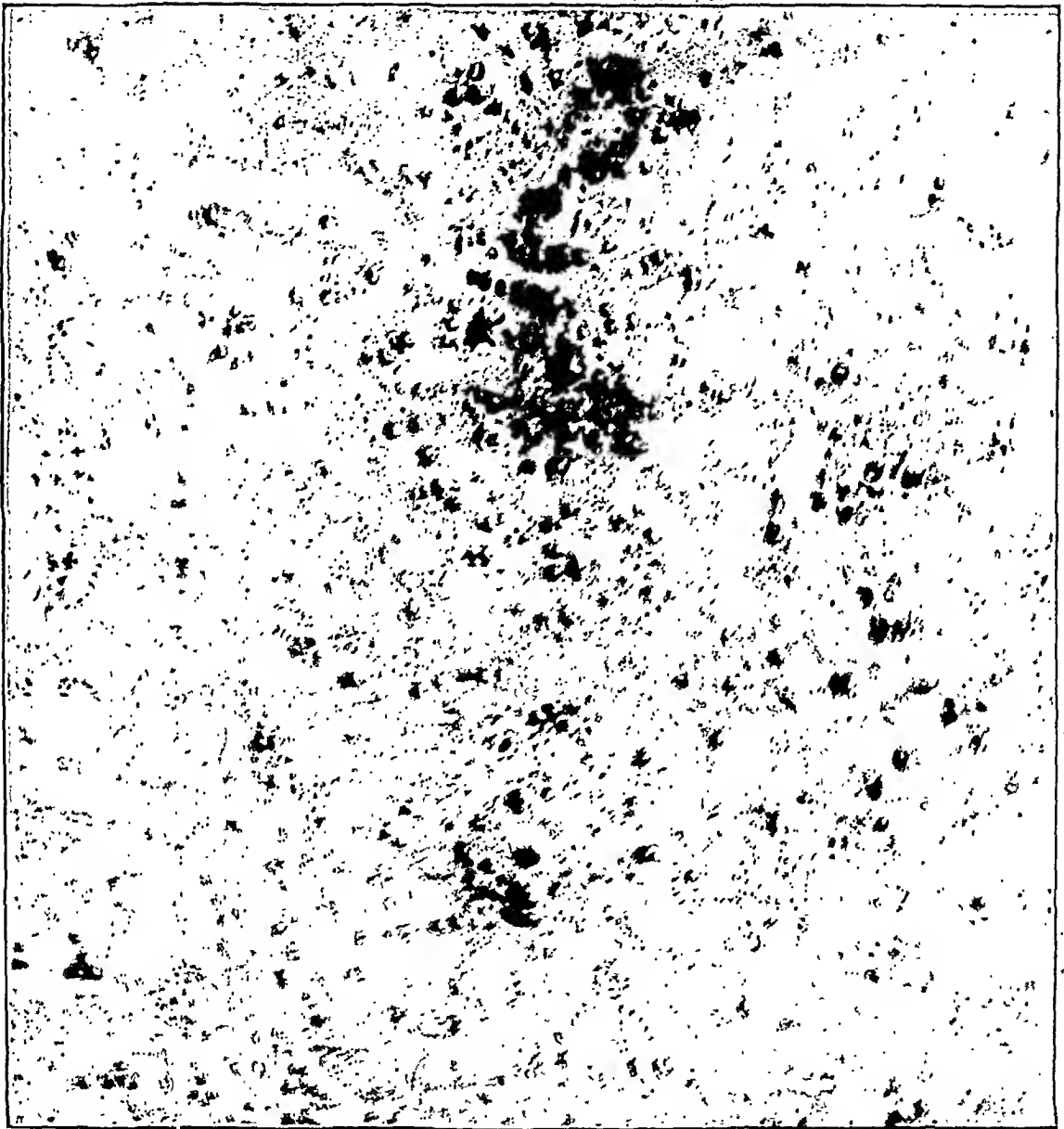


Fig. 6.— Patient, Case 1, skin of the back, showing multiple telangiectases.

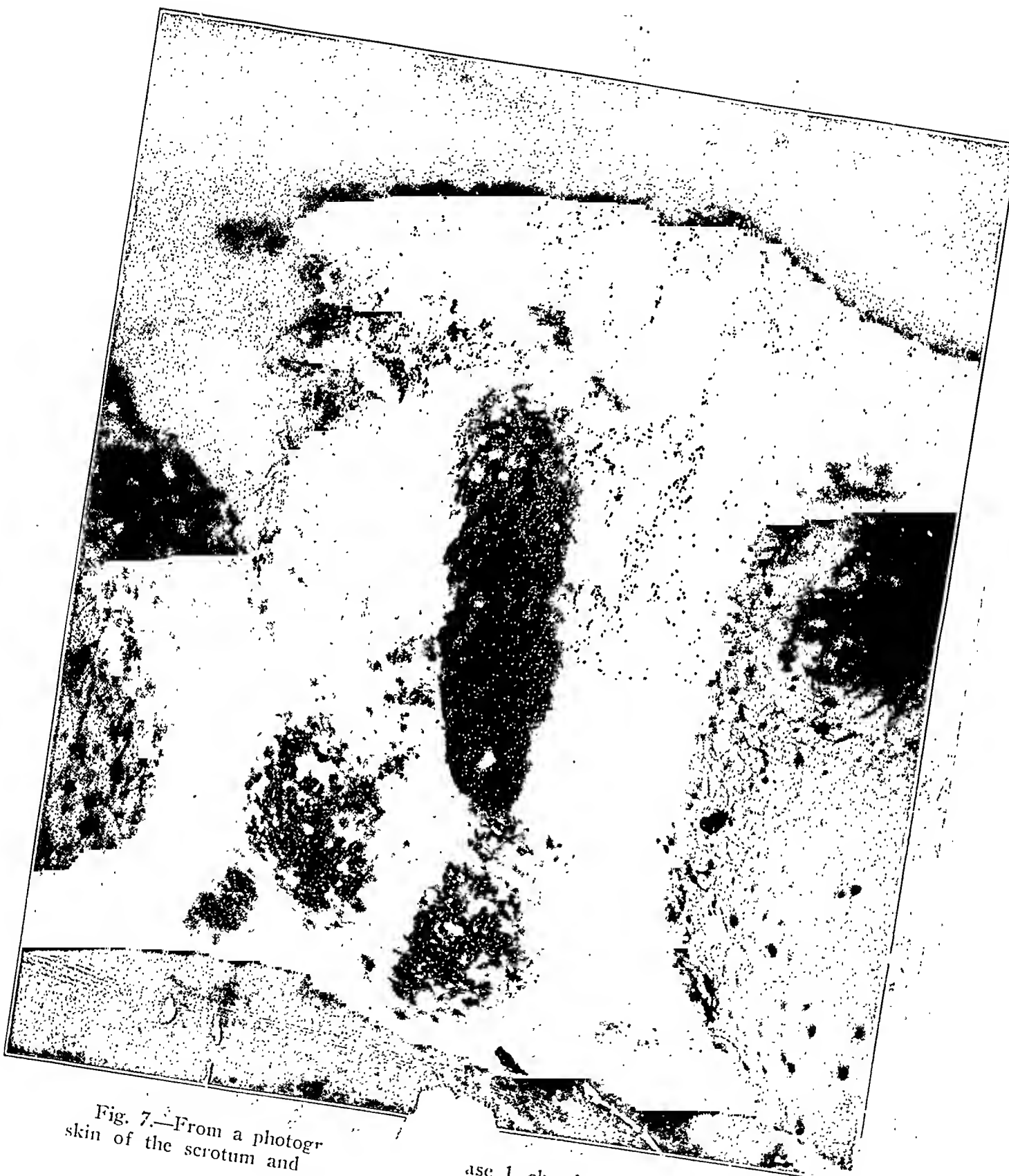


Fig. 7.—From a photogr
skin of the scrotum and

ase 1, showing hemangiomas of the
the thighs.

high color. The hair begins far back on the forehead; is thick and coarse; heavy eye lashes. Clinicians who examined the patient on previous admission agree that his features are larger and more prominent than before.

"In profile, the head has elongated, oval shape—narrow, prominent chin at one end of oval and crown of head at the other; large, wide nostrils. The nose looks narrow when protruded; shows indentation of teeth. Upper jaw is very broad at base, but narrowed in front by irregular placing of teeth; high palatine arch; front teeth widely spaced and irregularly placed in jaw; molars placed irregularly in jaw and of short, stubby type. Lower jaw narrow; teeth irregularly placed; some projected forward toward lips; others arranged regularly.

"In standing position patient is tall, stoop-shouldered; arms and legs look thin and long (Fig. 1); hands and feet of narrow type, fingers and toes long and tapering. Little fingers on both hands are deformed; tips of each curve inward toward adjoining finger, giving a bowed appearance. Joints of little fingers show no ankylosis, no exostosis.

"Thorax conformation broad at upper part, tapering somewhat at lower thorax, measures 88 cm. in circumference above, and 78 cm. in circumference of lower thorax.

"Abdominal conformation normal; no muscular rigidity.

"Nails long and tapering; convex and smooth.

"Hair over whole of body very light, thin and short. In axillae, groins and over scrotum, hair is black and coarse; well developed.

"Patient states that he does not sweat easily—only a very little in hot weather under arms; skin smooth and thin; free from pigmentation."

A careful physical examination of the patient was again negative for organic disease. The remarkable development of capillary vessels in the skin previously noted was present, vessels in increased numbers being found in the locations formerly described. Neither in color nor in size was any important change to be made out.

The patient remained on the medical service fourteen days. During this period he complained much, at times, of pain in the arms and legs. He did not lose weight. He was finally transferred to the surgical service where the hernia was repaired and the patient discharged.

CASE 2.—History.—Ole M., man, aged 60, single, American, laborer, was admitted to the University Hospital May 26, 1914, complaining of dyspnea, cough and swelling of the legs.

The patient's family history was unimportant, except that his father and one brother had died of tuberculosis of the lungs. As a child he had had whooping cough and mumps; also had articular rheumatism at 20 years of age. He denied lues. There was no history of nosebleed.

The history and clinical notes of the patient's present illness, dealing with the cardiorenal features of the case, and apparently having no bearing on the condition about to be described, will be omitted from this report.

The clinical diagnosis of myocarditis of the mitral valve, cardiac hypertrophy and dilatation, passive congestion of the liver and lungs, covers this part of the clinical study of the case.

The chief interest centers in the acromioclavic features associated with hemangiomas on the skin of the scapular and clavicular regions of the neck and lips. Just when these first appeared the patient could not state with certainty. He first noticed them about six years prior to admission. He did not remember exactly when his hands and feet began to increase in size. He was certain that they were larger ten years previously and that his features, especially the nose, had increased during the previous two years.

The man was of a stocky and short gorilla type of build. His speech was slow. All his movements were sluggish. The head was large and broad between the shoulders; forehead sloping and broad; broad, low forehead; short, broad abdomen; large joints; broad,



Fig. 8.—Ole M., Case 2, from the University Hospital, patient with acromegaly, showing hemangiomas of the mucous membrane of the lips. Note also the spacing of the teeth and the corrugated appearance of the under lip on the left side.



Fig. 9.—Case 2, showing

of the skin of the scrotum.

a fairly isolated position, for across the avenue, as well as on the other three sides, for some little distance, there are open fields. The house is provided with all modern conveniences. The sewage disposal system connects with that of the city. The water is also derived from the city supply, although the drinking water used by the majority of the families in the house was obtained from a spring in the immediate neighborhood. There is no public dining room. The families living in the house obtained their groceries and meats chiefly from a store in the neighborhood, though to a considerable extent also from the stores and markets in the central parts of the city; their milk from the various dairies of the city and their ice from a common source.

The thirty families which occupied the house consisted at the time of the outbreak of about seventy adults and eighteen children, the latter varying in age from infancy to 13 years. So far as the children were concerned, it may be said that they formed a society of their own, playing with each other in and about the house, not often going elsewhere or receiving visitors from without. But it was evident that the little community of children was isolated only in a comparative sense, for plenty of lines of communication with the outside world remained open, along which the infection might have found its way to them.

Although all the children in the X House inevitably came into contact with each other, since they lived in the same building and shared a common playground, yet on account of differences or similarities in age and taste, and for various other reasons, some had little or nothing to do with the rest, while others moved in small groups or cliques. Maude S, Nancy H, Jenny J, Fritzie H and J. N. (a boy who used to come from the city to play) were older and had little to do with the others. William S, who seems to have been *persona non grata*, usually remained alone with his nurse, and Dick E was purposely kept from the others by his parents. Baby B and Baby A were infants in arms. The remaining eleven children were also more or less subdivided into twos and threes. Jack C and Elizabeth D were inseparable; Fritzie H and Charlie B were almost constantly together, etc. The four older B children and the two C children, on the other hand, played little with each other and did not go to each other's apartments, and Ned F did not have much to do with the B's, but sometimes played with the C's. But all of these eleven children had this in common, that they were on especially friendly terms with the A children and frequently visited the A's apartment. In this sense it is possible to divide the children in the X House into two groups, the one group visiting the A's apartment and centering about A's, the other group not having these relations.

The A's apartment, situated on the ground floor of the X House, was readily accessible from the lawn. Mrs. A was exceptionally kind

to the children and gave them butter-bread or wafers when they came even to the door, and her own children were especially popular, with the result that the A's apartment and back porch became a favorite rendezvous. Ned F, the great friend of Harry A, used to "spend his entire time there"; the B children, except the baby, were very frequent visitors *en masse*, and often the two C children and Nancy H used to come. The A children had many toys — dolls, stuffed monkeys, Teddy bears, balls, tin horns, scissors for cutting paper dolls, etc. — and allowed all the visiting children to use them, so that the toys passed from one to the other, and were, in the A's apartment, common property. The games that were played were the games of children everywhere. It should be mentioned, however, that on the lawn there was a sandbox, about 8 by 8 feet, which was used by almost all the children in the X House, even by the older children; Dick E and William S used to be taken there when the others were not present.

Sept. 15, 1916, the case which we regard as the first of infantile paralysis made its appearance among the children in the X House. On the evening of this day, Harry A, aged 2½ years, was taken ill. September 11, five days previously, both he and his sister, Barbara A, 3½ years old, had what their parents regarded as a "digestive upset," accompanied by rather high fever. But both children were so much better on the following day after castor oil that they were considered well again. Harry A remained in normal health from that time until the beginning of his acute illness, five days later. He went to bed to all appearances perfectly well, but was found at 11 o'clock, screaming with pain. He was nauseated and vomited. His temperature was 103 F.³ All night he was extremely restless, slept fitfully and frequently cried out. The next day, September 16, he seemed extremely ill. His temperature was 103. The parents now noted something never seen in any of his previous illnesses and remarked on it at the time as being strange: that he cried whenever touched or moved, and put his hand frequently against the back of his neck. At times he seemed "out of his head." September 17, the third day of his illness, he was seen by the family physician, who was said to have made a very casual examination, and who left the impression that the illness might be a "bilious attack" or "malaria" (no blood examination was made). His temperature was then 102 F. The sensitiveness to touch continued. For the next three days Harry A remained in bed (or on a couch in the living room), except twice, when taken out for a drive. On the fourth day his temperature began to fall and his condition steadily improved. During this time the parents observed that, when he was taken out of bed, he was unable to climb back into it, and that he could get on his hands and knees but had difficulty in sitting up. When Harry A was strong enough to walk the parents became troubled at his way of doing it, and on September 23, the eighth day of his illness, made him walk before Mr. B, in order to obtain the latter's opinion. September 24, the ninth day of his illness, they consulted their physician, who, however, did not find anything wrong (according to the parents he did not test the child's reflexes). After that time the little boy rapidly recovered his former strength and is now perfectly well, except that he becomes fatigued easily when walking. Apparently the possibility of poliomyelitis was not suspected, and no physical examination with that in mind was made.

Either on the day following Harry A's illness or two days later (Mrs. A does not remember which) Baby A, aged 4½ months, developed a fever of

3. All temperatures are mouth, except in the case of Baby B, which are rectal.

103 F., and vomited. She is said not to have had fever previously but to have been subject to indigestion from birth, was malnourished and vomited frequently. Her temperature did not become normal for ten days. The baby was not seen by a physician.

Barbara A remained well during this time.

Illness next appeared in the B family, which consisted of Mr. and Mrs. B, a foreign white maid and five children. They lived on the ground floor of the X House. Mr. B used to go in the street cars each day to his laboratory in the city, where, however, he was not exposed to poliomyelitis or any other disease. Mrs. B and the maid, who spoke no English, remained at home practically the entire time. All three were in perfect health during the month which preceded the children's illnesses. They had one guest during the summer, but he had left more than a month previously. It is an interesting fact, as possibly indicating a predisposition to poliomyelitis in the B family, that one of Mrs. B's sisters and one of her cousins are paralyzed as the result of poliomyelitis in infancy.

As already mentioned, the children of the B family were particularly intimate with the children of the A family, and frequently visited the latter. September 16, the second day of Harry A's illness, Bobby B went to see Harry A and spent the entire morning playing with toys in the A's apartment. On the following day, September 17, Charlie B twice brought broth for Harry A and was in the A's apartment a half hour. He "caressed" Harry A but did not kiss him. On the following day or the day after, either September 18 or 19, the parents cannot remember which, Charlie B, Dorothy B and Mary B visited the A's apartment in order to see Harry A, and spent a half hour or more playing, and while there received buttered toast prepared for them by Mrs. A. It is thus seen that the contact between the B children, with the exception of the B baby, and the A children during Harry A's illness is very definite. The exception of the B baby to this contact is important, because the B baby was the only one of the B children who, within the nine days following the onset of Harry A's illness, did not contract poliomyelitis. For the two weeks previous to their illnesses the B family were not exposed, to their knowledge, to any sick person with the exception of Harry A and Baby A.

September 21, five days after the onset of Harry A's illness, Bobby B, aged 6½ years, was taken sick. That morning he had eaten a good breakfast and had been roller-skating for two hours, when he came into the house complaining that he felt sick and his head ached. His temperature was found to be 103 F. He went to bed seeming "a little dull," and refused dinner, but got up in the afternoon in order to see his teacher. He had a poor appetite for supper, and went to bed again immediately afterward. The next morning, September 22, he seemed so much better that his parents did not think it necessary to take his temperature and regarded him as being practically well. After a rather poor breakfast he went out of doors and remained there almost the entire day, the greater part of which he spent in roller-skating, coming in only for his dinner. Though he did not seem actually sick, he looked pale and did not act like himself. He went to bed without eating supper. The following day, September 23, he ate a good breakfast and went out roller-skating again, but returned at 11:30 looking very ill. It seemed to his parents that a sudden change had taken place; his temperature was 103 F., and he again complained of severe headache. He was put to bed at once and soon became so drowsy that it was necessary "to shout" to get an answer. He now began to complain of pain in the back of his neck and in the front of his head, and at 7 in the evening he vomited. The following day, September 24, he seemed slightly better and no longer complained of headache, and played with paper dolls. His temperature was 102.5 F. When seen late that afternoon by one of us, he was in bed, rational, and did not complain of pain, but looked extremely sick and exhibited the restless behavior of children with a high fever, though his temperature was only 102.5. His face underwent

frequent choreiform-like contractions. Some nasal obstruction was present, but unaccompanied by discharge. The knee and ankle jerks were exaggerated. No clonus was present. On attempting to obtain the Kernig sign, marked pain was elicited. There was general hyperesthesia; otherwise the physical examination was negative. That evening he became much worse, complaining of pain everywhere, and evidently paralysis had begun to manifest itself, for he could not stand. The following morning, September 25, he was again seen by one of us. His legs were almost completely paralyzed, though some slight motion of the left great toe was still present. Knee and ankle jerks were now absent. The diaphragm seemed to be completely paralyzed and thoracic respiration was feeble. Each inspiratory movement was accompanied by marked dilatation of the nostrils and gasping movements of the mouth. Slight internal strabismus had appeared and the left pupil was smaller than the right. About 1:30 p. m. there was a general convulsion. From this time on respiration was kept up by means of a "pulmotor." He was transferred to the poliomyelitis hospital. On arrival, spinal fluid was obtained, which showed 250 cells and a positive reaction for globulin. He was given 10 c.c. of immune serum intraspinally. He died at 1:30 the following morning.

At necropsy the typical lesions of acute poliomyelitis were found. There was a general lymphatic hyperplasia, most marked in the solitary nodule of the large and small intestines, Peyer's patches, and the mesenteric lymph nodes. The brain was soft and congested. The pons, medulla and spinal cord were swollen and edematous. There was a sterile fibrinopurulent exudate over the surface of the spinal cord (injection of immune serum). Microscopic examination showed hyperemia; extensive perivascular and diffuse infiltration of cells, mostly mononuclear, nerve cell degeneration and neurophagocytosis in the tegmenta of the pons and the medulla, and especially the anterior horns of the entire cord.

September 23, two days after Bobby B. was first taken sick, at about 10 o'clock in the evening, it was noticed that Mary B., aged 2½ years, did not seem well. The next morning, September 24, her temperature, taken for the first time, proved to be 103 F. Since her parents found it difficult to keep her in bed, they dressed her and allowed her to sit or wander about the house throughout the day. When seen by one of us in the late afternoon of September 24, her temperature was 102.5. She looked pale but did not act especially sick, did not complain, and gave no indication of headache. No examination was then made except to determine that both knee jerks were present but not active, that no paralysis existed and that her throat was clear. Her gait was normal. The next day, September 25, she seemed somewhat better, but was removed to the poliomyelitis hospital. On her arrival there she was very drowsy and irritable when disturbed; her temperature, however, was 99. Physical examination revealed nothing. A spinal puncture was made; the fluid obtained contained a trace of globulin but only five cells per cubic millimeter. (The physician who made the puncture is certain that there was no admixture of blood).

Three days after the beginning of Bobby B.'s illness and on the day following the illness of Mary B., namely, September 24, Charlie B., aged 9½ years, was suddenly taken ill. Charlie B. had eaten a fairly large breakfast that morning and had been out of doors playing, but returned to the house about noon, complaining of severe headache. His temperature was 103 F., and he was immediately put to bed. When seen late that afternoon by one of us his temperature was still 103; his face was flushed. He lay in bed, appearing in great distress, with his hand pressed against his forehead. He continually tossed about and his face twitched. On examination it was noted that the knee jerks were hyperactive; well marked hyperesthesia was present, and flexion of the extended leg in the attempt to obtain Kernig's sign seemed to produce a great deal of pain. The neck was not stiff, and in other respects the physical examination was entirely negative. On the morning of the next day, September 25, the temperature was 102 but his condition was greatly improved. He was found

sitting up in bed, cutting out paper dolls, and said his headache had entirely disappeared. A leukocyte count taken at this time showed 19,000 white blood cells. The physical examination was entirely negative, except that the knee jerks were still overactive. That afternoon about 2 o'clock he was transferred to a poliomyelitis hospital with his brother and two sisters. On arrival his temperature was 99.2 and lumbar puncture showed five cells and a negative reaction for globulin. Eight cubic centimeters of immune serum were given, however, intraspinally. The urine contained albumin. The boy quickly recovered his normal condition. A lumbar puncture repeated October 11, seventeen days after the onset of his illness, showed a clear fluid, which gave a negative globulin and contained only two cells to the cubic millimeter.

At 5:30 in the afternoon of September 24, Dorothy B came into the house complaining of headache. She had been out of doors almost the entire day, had eaten her usual dinner, and seemed in customary health. Her bowels had moved normally. Her temperature was immediately taken and found to be 104 F. She was put to bed. Her face was flushed. She seemed to her father very ill. She held her head and complained of headache exactly as her brother Charlie B had done. On the following morning, September 25, she was seen by one of us. A physical examination revealed nothing excepting overactive knee jerks. She was found sitting up in bed and said that her headache was gone. Her temperature was then 102.5. At 2 o'clock in the afternoon she also was taken to the poliomyelitis hospital. On admission her temperature was 101.6; pulse 140. Physical examination was negative. The spinal fluid showed three cells per cubic millimeter, and a negative test for globulin. She was given, however, 10 c.c. of immune serum intraspinally. The following day her temperature was normal. October 11, seventeen days after the onset of her illness, spinal fluid was again obtained; it contained nine cells per cubic millimeter and the test for globulin was negative.

September 24 the illness appeared also in the C family. The C family was composed of Mr. and Mrs. C, Mrs. C's mother and two children, Jack and Billy. At this time they had no servant. Mr. C, a business man, went to his work daily, using the street cars. Mrs. C and her mother had been out of the house very little during the two weeks which preceded Jack C's illness. Neither Mr. C, Mrs. C, nor Mrs. C's mother had been exposed to any illness so far as they were aware, and the children had not been in contact with any sick person except Harry A.

Jack C was 6 years old. About a week before the beginning of his acute illness he had a digestive upset (a frequent occurrence). This kept him in doors until September 21. On that day his physician allowed him to go out. In the morning he and his brother, Billy C, were taken for a half hour's drive by Mrs. A in the governess' pony cart, together with Elizabeth D, Barbara A and Harry A. It was the fifth day of Harry A's illness and he was still so weak that he had to be lifted in and out of the pony cart. Mrs. A, who drove, recalls that Elizabeth D and Barbara A, who were seated in the pony cart next to Harry A, quarreled so much that she removed Elizabeth D, putting Jack C in her place, so that Jack C and Harry A sat next each other for the greater part of the drive. Mrs. A says that the only reason she remembers the incident is that, when Jack C was placed next to Harry A, she noticed that both children looked pale. Mrs. A also says that the pony cart was so small and on this drive so crowded that all the children sat with their heads close together. Jack C was not exposed to any sick person during the two weeks preceding his acute illness except to Harry A on this occasion.

At 2 o'clock in the morning of September 24, the day on which Charlie B and Dorothy B were taken sick, Jack C awoke his parents complaining of headache, and shortly afterward vomited. His parents took it for granted that Jack C was suffering from another of his digestive upsets, but by the next morning, September 25, his condition had become so serious that they called

in their family physician. Jack's temperature was then 102.5 F.; the headache had become more intense and vomiting had recurred a number of times. When the physician arrived he found well-marked rigidity of the neck, increased reflexes, a positive Kernig sign and an extreme degree of hyperesthesia. The boy was extremely drowsy; occasionally he cried out in his sleep and twitched convulsively; at times he was delirious. September 27, the third day of his illness, a lumbar puncture was performed. The spinal fluid was sterile but contained 173 cells to the cubic millimeter, a preponderance of which were polymorphonuclear leukocytes, and the globulin test was faintly positive. At this time his temperature was 102.3 F. In the course of the next three days the temperature fell to normal and all symptoms disappeared. No paralysis developed. For the five weeks which followed he was kept in bed and the family have no idea whether any muscular weakness was present. He is now, January 1, entirely well.

The next child to be taken sick was Ned F, 3 years old. The F family was composed of Mr. and Mrs. F, their only son, Ned, and two servants. For some time Mrs. F and Ned had been at a summer resort which was considered free from poliomyelitis. They had returned to the X House only seven days before Ned became ill. None of the adults in the family had been exposed to any sick person, so far as is known, and were themselves well previous to Ned's illness. Ned F, as will be remembered, was a special friend of Harry A, and during Harry A's illness Ned F was repeatedly in the A's apartment. Mrs. F took Ned F and Harry A for an hour's drive in her automobile on September 20, the fourth day of Harry A's illness. Harry A was so sick at the time that he was carried to and from the automobile. We could not learn that Ned F was exposed to any other sick child than Harry A.

We do not know the exact details of Ned F's illness. Indeed, at first it was denied altogether, and later, only the fact admitted. From other sources we have learned, however, that on September 25, the day on which the B children were removed to the hospital, Ned F was taken sick and vomited. At noon of that day Mrs. F, learning that the B children had infantile paralysis, in great excitement wrapped Ned in a blanket and left the city. She is reported to have said that Ned looked so sick that she could not understand how she succeeded in passing the officials at the railroad station; that he vomited several times that day and night and felt hot; that she was terrified, and that he did not seem well again for ten days. We also learned that Mrs. F said she felt perfectly sure Ned had the disease. At any rate, he did not develop any paralysis and is now well.

On the day on which the B children were removed to the hospital and Ned F was taken sick, Elizabeth D, aged 5, the only daughter of Mr. D, an employee of the X House, became ill. The D family lived in the basement of the X House, and consisted of Elizabeth D, her father and an aunt. We could discover little in regard to her or her family during the two weeks which preceded her illness. We cannot find that she entered the A's apartment or came in contact with Harry A during his illness except on one occasion, namely, during the half hour's drive in the pony cart on September 21, the fifth day of Harry A's illness. Her boon companion was Jack C, and, if Elizabeth D had poliomyelitis, we should expect to find that her exposure occurred at the same time as that of Jack C (see page 62).

We have very little information in regard to Elizabeth D's illness. Her father denied to us that she was sick at all, but he told at least three of the residents of the X House that she was "very sick" on the night of September 26, and that he was "scared for fear she had infantile paralysis" and, in fact, a resident in the X House informed us that he knew at the time that Elizabeth D was ill, because he was kept awake by her screaming. The doctor who visited Elizabeth D informs us that she had an earache. He did not examine her ear

drum and her ear never discharged. Whatever the nature of her illness, it is certain that she was suddenly taken sick coincidentally with the others.

The next child to become ill was Billy C, aged 4. It will be remembered that Billy C was present, as well as his brother, Jack C, on the drive in the pony cart with Harry A. September 28, four days after Jack C's illness began, Billy C was suddenly taken sick. The evening preceding, the family doctor saw him and testifies that he was in normal health. At 1 o'clock in the morning he awakened his parents complaining that he could not sleep. At 8 o'clock he vomited. His temperature was then between 104 and 105 F. He had no headache but complained of pain in the back of his neck. When seen by the physician, the neck was rigid, the Kernig sign positive; the tendon reflexes were exaggerated; marked general hyperesthesia was present. At times he was delirious. In fact, his illness was more severe than that of his brother. At the end of six days his symptoms had entirely disappeared and no paralysis occurred. He, too, was kept in bed for five weeks, at the end of which time he seemed to have recovered entirely.

Baby B, the only one of the B children who had thus far escaped infection, was a healthy baby, 4½ months old, but weighing only 9 pounds. Her mother used to keep her out of doors on the lawn in a basket for a large part of each day when the weather was pleasant, but had not done so during the nine days which preceded her illness, because of the illness of Bobby B and the other children. Baby B's brothers and sisters came into the closest contact with her, and of the four, Bobby was the most devoted to her, often kissing and caressing her. Dorothy B frequently carried the baby about in her arms, and in the early morning it was the parents' custom to take the baby into their own bed, where the other children gathered to play with her. The parents vividly recall that on September 22, during the intermission which ensued between the acute symptoms of the onset of Bobby B's illness and those which preceded his death, he repeatedly kissed and fondled the baby.

Immediately preceding her acute illness Baby B was perfectly well, except for a slight cold, and did not come in contact with any sick person except her brothers and sisters.

At 6 o'clock in the evening of October 1 the baby was exhibited to a guest, a physician, and gave every sign of being in perfect health. At 10 o'clock Mrs. B observed that the baby's skin felt hot, but did not take her temperature, for lack of a thermometer. The baby took the 10 o'clock feeding well, but afterward seemed very sick, sleeping hardly at all and frequently crying out as if in pain. The parents, alarmed, remained awake the entire night. The following morning, October 2, the baby's temperature was found to be 102.5 F. She was exceedingly restless and very hyperesthetic. Her bowels moved normally and there was no vomiting. Late in the afternoon of October 2, the baby was seen by one of us. She looked very ill, frequently crying out, and screamed when touched. The fontanel was full, the pulsations particularly pronounced. Retraction of the neck was apparent and when the head was flexed on the chest, she screamed, though she did not resist the flexion. The knee jerks were much exaggerated and the ankle jerks easily obtained, but there was no clonus and no Kernig sign. No paralysis was present. A lumbar puncture was twice done and bloody fluid obtained, under apparently normal pressure. That evening the temperature rose to 103.6 F. By the following morning, October 3, the third day of the disease, paralysis had appeared, with involvement of the left deltoid, pectoralis major and triceps muscles. On this day the baby was removed to a poliomyelitis hospital. On arrival a lumbar puncture was performed; the clear fluid obtained contained 270 cells to the cubic millimeter and remained sterile. During the course of the day, weakness developed in the flexor muscles of the left leg. The temperature continued elevated for four days and then fell to normal. The baby still (Jan. 1, 1917) has paralysis of muscles of the left arm.

Thus, of the eleven children who formed the group which came into especially intimate contact with the A family, all but two developed some kind of an illness within a week of each other and within the thirteen days which followed the onset of Harry A's illness. The two who escaped were Barbara A, Harry A's sister, and Fritzie H. Barbara A was, of course, more exposed to infection, provided it centered about her brother or in the A's apartment, than any other child in the X House, and ought under those circumstances to have contracted the disease before any of the others.⁴ We cannot find that Fritzie H, on the other hand, entered the A's apartment at all or came in contact with Harry A during his illness, and if exposure in the A's apartment or to Harry was essential for infection, ought to have escaped it. She was exposed, however, to Bobby B on September 22, the day marking the intermission period of his illness, for on that day she was taken on a drive with him and Barbara A in the A's pony cart; but she remained well (Table 1).

EXPERIMENTS

The following experiments were planned with a view to proving that certain of the cases of illness among the children in the X House, not accompanied by paralysis, were poliomyelitis, and in the hope that by the method employed we might be able to trace the outbreak back to its starting point.

EXPERIMENT 1 (a).—Oct. 13, 1916. *Ringer solution washings of the nose, mouth, pharynx and intestines of Charlie B, obtained when in perfect health, nineteen days after the onset of his illness; the filtrate injected into a monkey.*

The washings of nose, throat and mouth were made by passing the Ringer solution through these passages several times, until it was rich in mucus. The intestinal washings were obtained in a similar manner, after the fecal matter had been removed by means of a normal saline enema. Both sets of washings were mixed together, shaken and passed through a Berkefeld filter, which would not allow the passage of the *B. violaceus*. Fifty cubic centimeters of filtrate were obtained, 2 c.c. injected into the left lateral ventricle, and 10 c.c. into the peritoneal cavity of *Macacus rhesus* 1, a small monkey which had been in the laboratory about four years. The monkey appeared healthy. The injections were made under ether anesthesia.

This monkey recovered at once and remained well for forty-eight hours. He then showed weakness in his right hind leg, later in his left hind leg, and a prolapse of the rectum developed. He dragged his hind parts. On the fourth day his front legs became weak and his respirations rapid. He was unable to lift himself from the floor. He was not, however, completely paralyzed in any of his extremities. On the fifth day his respirations became slow and labored and he died. At necropsy, no lesions of the organs were found excepting hyperplasia of the lymphatic nodules of the spleen, stomach, intestines,

4. It will be remembered that Barbara A was ill on September 11, with a temperature of 104 F. It is possible that she had poliomyelitis at that time, but scarcely probable, because her illness was in no way typical and could be explained on dietetic grounds.

TABLE 1.—INDICATING AGE AND FAMILY GROUPING OF CHILDREN AND EXPOSURE TO AND INCIDENCE OF POLIOMYELITIS AMONG THEM

Children of	Age, Yrs.	Exposure to Harry A or His Immediate Environment	Poliomyelitis	Unexplained Illness Occurring Coincidentally with the Cases of Poliomyelitis	No Illness	Outcome Form of Disease
A Family						
Barbara	3½	+ ¹	+	
Harry	2½	..	+	Recovery; nonparalytic
Baby	1½ ²	+	..	+ ³	..	Recovery
B Family						
Charlie	9½	+	+	Recovery; abortive
Dorothy	8½	+	Recovery; abortive
Bobbie	6½	+	+	Death; ascending paralysis
Mary	2½	+	+	Recovery; "masked" form
Baby	1½ ²	— ⁴	+	Recovery with paralysis
C Family						
Jack	6	+	+	Recovery; nonparalytic form; spinal fluid
Billy	4	+ ⁵	+	Recovery; nonparalytic
D Family						
Elizabeth	5	+	..	+ ⁶	..	Recovery
E Family						
Dick	2	—	+	
F Family						
Ned	3	+	..	+ ⁷	..	Recovery
S Family						
Maude	13	—	+	
William	5	—	+	
H Family						
Nancy	8	—	+	
Fritzie	12	—	+	
J Family						
Jenny	12	—	+	
N Family						
J N ^s	12	—	+	

1. See footnote 4.

2. Four and one half months.

3. See pages 59 and 64.

4. But exposure to brothers and sisters; see page 64.

5. See page 63; and to Jack O.

6. See page 63.

7. See page 63.

8. J N does not strictly belong to the group of children in the X House. See page 58.

lungs and lymph glands. The brain appeared normal. The cord was hyperemic but not edematous. There were a few hemorrhages into the cord and medulla, but no cellular infiltration, except in one small area in the floor of the fourth ventricle. A small part of the floor was infiltrated with round cells, and a few of the neighboring veins showed perivascular infiltration. A number of the sensory ganglia were examined, but no lesions were made out. A piece of the cord was taken aseptically and placed in 50 per cent glycerin.

EXPERIMENT 1 (b).—Dec. 2, 1916. *Injection of an emulsion in physiologic salt solution of the glycerinated cord of Monkey 1 into Monkey 2, a healthy Macacus rhesus.*

One cubic centimeter was placed in the left lateral ventricle and 4 c.c. in the peritoneal cavity of this monkey.

EXPERIMENT 1 (c).—Dec. 12, 1916. *A thick emulsion in physiologic salt solution of another part of the glycerinated cord of Monkey 1, injected into Monkey 5.*

One cubic centimeter of the emulsion was placed in the left lateral ventricle and 1 c.c. in the peritoneal cavity.

Both of these monkeys remained well up to the time of writing, Jan. 22, 1917.

EXPERIMENT 1 (d).—Oct. 29, 1916. *Nasal, pharyngeal and intestinal washings again taken from Charlie B and from his sister, Dorothy B, thirty-five days after the onset of their illnesses, and injected into monkeys.*

Nasal and pharyngeal washings of the two children were mixed together, filtered, and 2 c.c. of the filtrate were introduced into the left lateral ventricle and 10 c.c. into the peritoneal cavity of a large, healthy monkey, 4.

The intestinal washings of the two children were kept separate, shaken and filtered and injected in the same manner, each into one of a pair of young healthy *Macacus rhesus* Monkeys 5 and 6. These monkeys were well at the end of six weeks.

EXPERIMENT 2.—Oct. 21, 1916. *Washings of the nasopharynx, mouth and colon of Harry A obtained in manner described in Experiment 1, thirty-six days after the onset of his illness, injected into large Macacus rhesus 3.*

Two cubic centimeters were injected into the left lateral ventricle, 40 c.c. into the peritoneal cavity. The filtrate contained very little mucus. The monkey was reported to have remained well.

DISCUSSION OF EXPERIMENTS

Flexner and Lewis found that the filtrate of an emulsion of the nasal mucous membrane of a monkey having poliomyelitis produced the disease when inoculated into a healthy monkey. Following this experiment a number of investigators, Landsteiner and Levaditi, Leiner and v. Wiesner, Römer, Strauss, Rosenau, Sheppard and Amoss and Gins,⁵ attempted to transmit the disease to monkeys by means of a Berkefeld or Chamberland filtrate of material obtained from the nose, pharynx or mouth of patients ill with the disease. All the experiments were negative.

In February, 1911, Osgood and Lucas⁶ reported successful transmission of the disease to healthy monkeys by means of a Berkefeld

5. See Kling, Pettersson and Wernstedt (Footnote 7) for references to authors just cited.

6. Osgood and Lucas: Transmission Experiments with the Virus of Poliomyelitis, Jour. Am. Med. Assn., 1911, 56, 495.

filtrate of an emulsion of the nasal mucous membrane obtained from monkeys dying without other demonstrable infection six weeks and five and one-half months after the acute stage of the disease.

By far the largest number of experiments of this kind were performed by Kling, Pettersson and Wernstedt,⁷ 1912. They attempted to transmit the disease to monkeys by means of a filtrate of the secretion of the nose, mouth, pharynx, trachea and intestines of persons dead with the disease, acutely ill with it, having recently recovered and having recently been exposed to it, and healthy persons who apparently had no contact with the disease. These investigators report a large number of positive results. The technic they used differed in one important particular from that of their predecessors; instead of a Berkefeld, Chamberland or other filter, they used a Heim, which is more permeable.

In 1913, Flexner, Clark and Frazier⁸ washed with normal saline solution the nose, mouth and pharynx of healthy parents of a child sick with the disease. The solution was shaken and passed through a Berkefeld filter. One and a half cubic centimeters were injected into the sciatic nerve and 140 c.c. into the peritoneal cavity of monkeys. They developed typical symptoms, and the authors assert that the cords showed typical and characteristic lesions of the disease.

It is thus seen that the disease has been successfully transmitted from infected human beings to monkeys. But the majority of investigators who have attempted thus to transmit the disease have been unsuccessful. Although Kling, Pettersson and Wernstedt report a large number of positive results, and that a high percentage of their inoculated monkeys showed symptoms certainly strongly suggestive of poliomyelitis, the positive interpretations which they put on the results of many of their experiments are open to criticism, in that they accepted purely degenerative changes in the nervous system as a final criterion for the diagnosis of this disease. In fact, the large number of positive results reported by Kling, Pettersson and Wernstedt are difficult to reconcile with the observations of Flexner and Lewis⁹ and other investigators, according to which monkeys frequently fail to become infected, even when an emulsion of the spinal cord of another monkey dead of the disease is used, and further, it is known that

7. Kling, Pettersson and Wernstedt: *Investigations on Epidemic Infantile Paralysis*. Report from the State Medical Institute of Sweden to the Fifteenth International Congress on Hygiene and Demography, Washington, D. C., 1912. Stockholm, 1912.

8. Flexner, Clarke and Frazier: *Epidemic Poliomyelitis, Fourteenth Note: Passive Human Carriers of the Virus of Poliomyelitis*, Jour. Am. Med. Assn., 1913, 60, 201.

9. Flexner and Lewis: *The Transmission of Epidemic Poliomyelitis to Monkeys*, Jour. Am. Med. Assn., 1909, 53, 1913.

human strains are often less virulent to monkeys than strains that have undergone preliminary passage through monkeys, which are more susceptible to the disease.

Negative results following the inoculation of monkeys with secretions which are supposed to contain the virus of poliomyelitis, mean nothing.

In our experiments the material was obtained three and six weeks after the acute stage of the disease and after the children had been well for some time. No attempt was made to concentrate the material, and the material injected was small in amount.

DISCUSSION OF DIAGNOSIS

The clinical diagnosis of poliomyelitis is ordinarily made when a flaccid paralysis suddenly develops without apparent cause in the course of a short, otherwise unexplained febrile illness, usually marked by symptoms of involvement of the central nervous system, and it receives corroboration if certain fairly characteristic changes also occur in the spinal fluid. The paralysis may be so extraordinarily distinctive in the suddenness of its development and selection of muscle groups as alone to establish the diagnosis, but the constitutional manifestations of the disease are never in themselves sufficient to distinguish it from certain other infections. Under unusual conditions, however, the circumstantial evidence favoring poliomyelitis may be so overwhelming as to justify that diagnosis when only the constitutional symptoms are present; that is, when poliomyelitis is in the community in epidemic form and side by side with the case in question, which cannot be explained otherwise; or when in the same family or house, or among playmates, manifest cases of the disease develop having identical onset and symptoms.

Such were the unusual conditions that obtained in the outbreak at the X House; 8 children living in the same house with definite association proved; all taken abruptly sick, without apparent cause, within fifteen days of each other, 6 of them within eight days of each other; 7 of them obviously having the same disease, as judged by the mode of onset, symptoms and physical signs, and 3 of the 7 proved to have poliomyelitis by the development of paralysis or changes in the spinal fluid.¹⁰

10. The correspondence in the symptoms shown by these children is most interesting. Harry A, Billy C and Jack C were each suddenly taken ill with high fever, vomiting, pain in the head and in the back of the neck, and hyperesthesia, and were at times irrational. All escaped paralysis. Their illnesses, which lasted five to six days, were so similar that the description of one serves for the other two. No other cause for their illness could be found,

The diagnosis of poliomyelitis in the case of Mary B, who did not show all of the symptoms of the others, depended on circumstantial evidence alone. It will be remembered that her illness was characterized only by fever, pallor and malaise. The onset may have been sudden, headache may have been present, but neither was apparent (she was only 2½ years old). The coincidence of her illness, otherwise unexplained, with the illnesses of her four brothers and sisters, leaves no alternative but to regard the illness as poliomyelitis also.

When we come to the illnesses of Ned F and Elizabeth D, it must be said that the data in our possession are insufficient to permit any positive conclusion. But we feel it is not without significance that these two children were abruptly taken sick, five to seven days after exposure to Harry A (Ned F at least, without apparent cause), and coincidentally with the six other children. Elizabeth D's "earache" might have been the violent headache which was so marked a symptom in the other cases. We can form no idea whether the illness of Baby A was poliomyelitis or not.

MODE OF CONVEYANCE OF INFECTION

Although now it is very generally believed that poliomyelitis is an infectious disease, there exists considerable difference of opinion in regard to its mode of conveyance from one person to another. The theory which has received most support from clinical experience and experimental investigations on monkeys is that the infecting material is contained in the discharges of the carrier of the disease and conveyed to the noninfected by direct contact, or through the medium of contaminated objects, such as toys, food, clothing, etc. (Wickman, Kling, Pettersson and Wernstedt, Flexner and others), or possibly through the agency of filth-carrying insects, such as the fly. But others have ascribed the conveyance of infection to blood-sucking insects.

dietetic or otherwise. The spinal fluid was taken in only one case (Jack C) and in that one case it showed the characteristic changes found in poliomyelitis.

Turning now to the B children, the illnesses of Dorothy, Charlie and Bobby, were absolutely identical up to the third day. The onsets were violent, timed to the half hour, marked by intense headache, high fever, extreme restlessness, hyperesthesia and increased tendon reflexes. After the initial stage the improvement was rapid. On the second and third days Bobby B went out to play. Dorothy and Charlie would have done so at the same period had they been allowed. The only difference in the illnesses of the three children was that Bobby B's symptoms started up again on the third day, while those of Dorothy B and Charlie B ceased altogether. No cause for their illnesses other than poliomyelitis could be discovered. Bobby B died of the ascending type of paralysis (necropsy). No wonder that Mr. B remarked, when his fourth child was taken ill: "I don't know what the matter with the children is, but I am sure that they all have the same thing."

The stable fly (Rosenau and Brues),¹¹ the bedbug (Howard and Clarke¹²), the rat flea (Richardson¹³) and other insects have been thought to be the agents of conveyance.

We investigated the question of insects and insect-carrying animals at the X House, but failed to find any evidence that insects could have been the source of the infection. The X House and its environs were probably as nearly free from them as any house or locality in the city. There were no fleas, and we cannot find that the stable fly was common in that locality. But aside from these considerations, the theory of the transmission of poliomyelitis by biting insects does not explain the facts of the outbreak at the X House; for one group of children was affected and the other spared; moreover, the children in the affected group developed the disease suddenly, six children (possibly eight) almost together, and the outbreak was begun and ended in two weeks.

We also investigated the sanitary conditions at the X House (garbage disposal, etc.), and the food and water supplies of the different families, without bringing to light any facts indicating the introduction of the infection through those channels. So far as we are aware, there was no single kind of food, or a food derived from a particular source, except perhaps sweetmeats, which was common to the affected families and not to any of the others. The case of the B baby, however, renders the food transmission theory untenable, in one instance at least, for the baby received different food from that of all the other affected children¹⁴ and yet contracted the disease.

The theory of infection through human contact, on the other hand, furnishes the likely interpretation of the facts.

If the analysis of the outbreaks of poliomyelitis in the X House indicates one thing more than another, it is that the primary spreading point of the infection was in the A apartment or connected in some way with the A family, in all probability centering about Harry A. The crux of the problem seemed to be, therefore, to discover how the disease found its way into the A family.

Mr. A was in the habit of going to his office in the city each day by the street cars, but was not aware of contact with any case of poliomyelitis or any sick person. Mrs. A left the X House very little during the period which preceded Harry A's illness, and met, to her knowl-

11. Rosenau, M. J., and Brues, C. T.: Some Experimental Observations on Monkeys Concerning the Transmission of Poliomyelitis Through the Agency of *Stomoxys Calcitrans*, Tr. XVth Internat. Cong. Hyg. and Demog., 1912, **1**, 616.

12. Howard, C. W., and Clark, P. F.: Experiments on Insect Transmission of the Virus of Poliomyelitis, *Jour. Exper. Med.*, 1912, **16**, 850.

13. Richardson, M. W.: The Rat and Infantile Paralysis; a Theory, *Boston Med. and Surg. Jour.*, 1916, **175**, 397.

14. The baby's food consisted of Walker-Gordon milk and lactose.

edge, no one who had poliomyelitis or any other disease. The colored maid,¹⁵ 19 years old; the laundress, also colored, who did her work outside the A's apartment; P. V., the boy who drove the pony cart, and P. V.'s friend, were each visited at their homes without bringing to light any association with any case of poliomyelitis there or elsewhere.

The only other person from without who came in contact with the A children during the critical period which preceded Harry A's illness was Mrs. A's father, Mr. W, an elderly man, a resident of New York, and accustomed to travel about extensively. September 6, nine days before Harry A was taken ill, he had come directly from New York, where poliomyelitis was then at its height, to visit his daughter, remained for a day and night in the A's apartment, and while there came in close contact with the children; in Mrs. A's words, "the children climbed all over him." But except for the fact that he came from an infected locality and that the date of his visit preceded the date of his grandson's illness by a comparatively short interval, there seemed to be little reason for supposing him to be the carrier of the disease. We desired to learn whether he had come into contact with poliomyelitis, or had been ill himself prior to his visit to his grandchildren, but were unable to obtain this information. We also sought to test him for poliomyelitis by the inoculation of monkeys with filtrates of his secretions, but without success. We were, therefore, unable to discover the origin of Harry A's illness and of the outbreak in the X House.

We think, however, we have obtained evidence that the disease was transmitted from person to person after it had found entrance to the X House. At least, we have been able to show that all those children developing the disease after Harry A were exposed to Harry A, with the exception of Baby B, and became ill with the disease from three to eight days after the exposure; that Baby B, on the other hand, was in her turn exposed to Bobby B and the other B children, and developed the disease less than nine days afterwards; that all the children exposed to Harry A during his illness developed the disease with the

15. Although we had no evidence to show that the colored maid was the carrier of poliomyelitis, we could not help but regard her with suspicion, because, on the one hand, she lived at home (going to and coming from her work at the A's apartment) in a negro district of the city, and, on the other hand, came into intimate contact, not only with the A children, but with almost all the children who were affected. She left the employ of the A's September 25, the day on which it became known that the B children had poliomyelitis. We visited her home on three different occasions and at the two places of employment which she had obtained after her departure from the A's, but were unable to find that she had been exposed to any case of poliomyelitis prior to Harry A's illness, or that any cases of the disease had developed among those with whom she came in contact after she left the A family, as might have happened had she been a carrier.

exception of Barbara A, Harry A's sister, and perhaps also Ned F and Elizabeth D,¹⁶ and that none of the children not exposed to Harry A (with the exception of Baby B, just mentioned), on the other hand, developed poliomyelitis.

A consideration of the incubation period of all the children calculated on the supposition that the outbreak took origin from Harry A or his environment, also lends support to this view (Table 2). The

TABLE 2.—GIVING THE EXPOSURE TO AND ONSET OF POLIOMYELITIS IN THE CHILDREN IN THE X HOUSE

September 15, Harry A develops poliomyelitis

	Bobby B	Mary B	Jack C	Charles B	Dorothy B	Ned F*	Elizabeth D*	Billie C	Baby B
9/16	Exp. A†	Exp. A?			
9/17	Exp. A	Exp. A	Exp. A?			
9/18	Exp. A	Exp. A	Exp. A	Exp. A	Exp. A?			
9/19	Exp. A	Exp. A	Exp. A	Exp. A	Exp. A?			
9/20	Exp. A	Exp. A	Exp. A	Exp. A	Exp. A			
9/21	Onset	Exp. A	Exp. A	Exp. A	Exp. A	Exp. A?	Exp. A	Exp. A	Exp. B
9/22	Exp. B
9/23	Onset	Exp. B
9/24	Onset	Onset	Onset	Exp. C	Exp. B
9/25	Onset	Onset	Exp. C	Exp. B
9/26									
9/27									
9/28	Onset	
9/29									
9/30									
10/ 1	Onset

* A definite diagnosis of illness not made.

† Exp. A = exposure to Harry A; Exp. B = exposure to the B children; Exp. C = exposure to Jack C.

shortest incubation period was that of Jack C (exposed to Harry A, September 21, during the drive in the pony cart); it was three days long. The incubation period of his brother, Billy C, was four days, if he acquired the disease from Jack C, seven days if from Harry A during the drive in the pony cart just referred to. His exposure to his brother, Jack C, was particularly close, because the family, not appreciating the nature of Jack C's illness for two days, made no attempt to

16. Ned F and Elizabeth D, it will be remembered, were both taken sick on September 26, four to seven days after their exposure to Harry A, but the data in regard to their illnesses were not sufficient to form a definite judgment.

keep the two boys apart during that time. Bobby B's incubation period was probably five days, though it may have been less. He came in contact with Harry A two to three days before his brother and sisters, and developed the disease two or three days before they did. This rather remarkable correspondence between the time of exposure and of onset made it seem likely that his infection dated from the first day of his exposure to Harry A, which would make the incubation period five days. The incubation periods of Mary B, Dorothy B and Charlie B, calculated from their exposure to Harry A, lie between two and seven days, and seemed fairly definite. (Of course it was possible that Mary, Dorothy and Charlie B contracted the disease from their brother Bobby B, but a consideration of all the facts makes that source of infection less probable.) Baby B's incubation period, calculated from her exposure to her brothers and sister, may have been as short as six days. The contact between her and Bobby B, in the intermission period of the latter's illness, was so intimate (he was repeatedly seen to kiss her) that we have felt inclined to date her infection from that time, which would make the incubation period seven or eight days; but she may have acquired the infection from Bobby B, or the other children later, or from infected material left by them in the apartment (see appendix). In general, it may be said that the estimated incubation periods of the children compare with each other in quite a remarkable way, and that the curve formed by plotting out the dates of known exposure parallels the curve representing the dates of onset as nearly as would obtain if the outbreak had been measles or scarlet fever instead of poliomyelitis. The average duration of the estimated incubation periods is four to five days.¹⁷

UNUSUAL FEATURES OF OUTBREAK

We wish now to point out several features of the outbreak of poliomyelitis at the X House which are of unusual interest. The first is the remarkable coincidence of the appearance of the disease in all 5 children of one family. Pasteur¹⁸ reported 7 cases in one family, 3 of which were of the paralytic form. The largest number of reported cases of poliomyelitis in any one family during the great New York epidemic of the summer of 1916 was 4.¹⁹ Reece²⁰ reported the develop-

17. In estimating the above incubation periods we are fully aware of the dangerous ground on which we tread, and wish it to be understood that we regard them only as probable.

18. Pasteur, W.: *An Epidemic of Infantile Paralysis Occurring in Children of the Same Family*, Tr. Clin. Soc. London, 1897, **30**, 143.

19. Emerson, Haven: Personal communication, 1916.

20. Reece: *Proc Roy. Soc. Med. (Epidem. Sec.)*, 1911-1912, **59**. Rep. Med. Officer, Local Govt. Board, 1912.

ment of 9 cases of poliomyelitis in an ordinary dwelling house, but involving more than one family.

Another interesting feature of the outbreak of poliomyelitis at the X House was the variety of forms in which the disease manifested itself. The case of Bobby B was of the fatal form of *ascending paralysis*. The cases of Harry A, Jack C and Billy C were typical examples of the *nonparalytic* form of the disease. The acute symptoms lasted the full period, five or six days, and their severity was such as to have warranted the assumption that paralysis would follow. The illness of Charlie B and Dorothy B, characterized by violent onset with symptoms suggestive of meningitis, but subsiding within forty-eight hours, are excellent examples of the *abortive* form of the disease. Mary B, on the other hand, represents "masked" poliomyelitis (the "larvierte" form of Müller). This case would never have been recognized except for its association with the others. It is these last two forms which Wickman and others regarded as a special menace to the community.

Another feature of considerable interest is the absence of changes in the spinal fluid in three of the cases, Mary B,²¹ Charlie B and Dorothy B. We cannot find in the recent literature a description of any case of poliomyelitis in which the spinal fluid was found to be normal. As a matter of fact, little is known about the spinal fluid in the abortive and "masked" forms of the disease, for the reason that a spinal puncture is almost never made in these cases.

The occurrence of so large a proportion of nonparalytic forms of poliomyelitis among the affected children in the X House is interesting and is probably not so unusual as might first appear, because the milder forms ordinarily escape recognition (Wickman,¹ Leegaard,²² Müller,²³ Kling, Pettersson and Wernstedt⁷ and others. A careful investigation by Wickman of separate outbreaks of poliomyelitis in small isolated Swedish villages for such cases revealed that 35 per cent., 46 per cent. and 56 per cent., respectively, of the total number of cases were nonparalytic. Wickman estimated that 50 per cent. of the cases in epidemics of poliomyelitis were nonparalytic. Leegaard expressed a similar opinion. Edward Müller, who investigated the epidemic of poliomyelitis in Hesse Nassau, Germany, in 1909, came to the conclusion that the abortive forms far exceeded the paralytic, and were especially common among adults. Reece, who studied the "Stokes

21. We should not regard the positive globulin without the presence of alterations in the cellular content as having any special significance.

22. Leegaard, Chr.: Kliniske og Epidemioliske Undersøgelser over der akuten Poliomyelit i Norge, Vidensk. Selsk. Skr., Christiania, 1909.

23. Müller, Edward: Die spinale Kinderlahmung—Eine Klinische und epidemiologische Studie, Berlin, 1910.

River epidemic" of poliomyelitis in England, reported thirty-three abortive cases of poliomyelitis out of a total of thirty-six. Kling, Pettersson and Wernstedt say, "According to our experience the virus carriers and the abortive cases in a family may be four to five times as numerous as the cases showing typical symptoms." And finally, even the statistics of the 1916 New York epidemic show that the nonparalytic cases have been more numerous than those showing paralysis. In the X House, the proportion of nonparalytic cases is over 60 per cent.

Finally, how can we reconcile the facts that in the outbreak at the X House the disease occurred in so severe a form in one case and so mild a form in most of the others? And, what is the significance when the incidence of the disease in a given community is high and the proportion of mild forms relatively great? We can only theorize in answer to these questions. We wish to point out, however, that the severity of the disease in the case of Bobby B may be explained on the ground of excessive physical exertion (it will be remembered that he roller-skated throughout the second and the morning of the third day of his illness). Wickman writes in this connection: "Exercise during the initial stage seems unfavorably to influence the further course of the disease and seems to tend to induce a relapse."

The significance of a high incidence of the disease in a community or a house must be that the infecting material is widespread and easily accessible, so that a large number of persons become infected. The significance of the large proportion of mild cases as observed in all the carefully studied epidemics we would regard as indicating that the larger number of persons are, under ordinary conditions, little susceptible to the disease. If it is true that relatively few are naturally susceptible, it should be found that when the incidence of poliomyelitis is high, the relative number of nonparalytic forms is high; that is, the two vary directly with each other, and the greater the one, the greater also the other.

In conclusion we wish to point out from our experience that a focus of infection in a city or in a house occupied by numerous families or in an institution cannot, from the nature of things, be ideal for the study of the epidemiology of poliomyelitis. The contacts are so numerous that the investigator, attempting to trace the path of the infection, becomes lost in a maze of difficulties. The ideal conditions for such a study are still to be looked for, as Wickman originally pointed out, in a thinly settled community in which contacts occur, but every one of these contacts is an event.

We wish to express our appreciation to Dr. Simon Flexner of the Rockefeller Institute for Medical Research, New York City, and to Dr. G. W. McCoy of the United States Public Health Service, Washington, D. C., for supplying monkeys for some of our experiments.

APPENDIX

We wish to put on record two experiments which were performed in reference to the mode of transmission of the virus of poliomyelitis.

Experimental Attempt to Demonstrate the Virus of Poliomyelitis in Monkey.—Through the health department, a considerable amount of paper and silver money was collected from persons in houses exposed to poliomyelitis. The money was collected in a large, clean, freshly-boiled museum jar which was fitted with a tightly fitting ground glass cover. It was placed directly in the jar by the person from whom it was collected. The money was shaken with a small amount of normal saline solution, the mixture filtered through a Berkefeld filter and the filtrate injected by Dr. G. W. McCoy into a brain ventricle and the peritoneal cavity of a healthy *Macacus rhesus* monkey. Dr. McCoy reports that this monkey did not show any symptoms.

Experimental Attempt to Demonstrate the Virus of Poliomyelitis in Dirt. (in association with Dr. Kenneth D. Blackfan).—Previous to the fumigation of the apartment, and just at the time of the removal (September 25) of the children from the B apartment to the poliomyelitis hospital, the room in which they had remained most of the time of their illnesses was carefully swept. The sweepings, which contained dust, lint, hair, hairpins and a few fruit seeds, were placed in a clean, freshly-boiled museum jar fitted with a tight cover. The material was dry and small in amount.

October 18, the sweepings were covered with a small amount of normal saline solution and left to soak over night in the laboratory. On the following day the mixture was shaken and filtered through a Berkefeld filter. Under ether anesthesia, 2 c.c. of the filtrate were placed in the right lateral ventricle, and 5 c.c. into the peritoneal cavity of a small female *Macacus rhesus* monkey, No. 8. This monkey had been in the laboratory for about four years. She appeared healthy.

The monkey remained well for two days after the injection, at which time she became ill and showed weakness in her left hind leg. On the third day her right hind leg was also weak, and when moving she dragged her hind parts. The illness in every way appeared to be comparable to that observed in Monkey 1. She did not, however, develop any prolapse of the rectum. On the fourth day she appeared very ill, her respirations were rapid—50 per minute.

While under observation at this time she fell, fracturing her skull.

At necropsy the internal organs appeared normal, except for hyperplasia of the lymph node of the intestines, spleen, lungs, mesenteric and bronchial lymph glands. The lumbar and dorsal cord was hyperemic and edematous and there were small hemorrhages in the gray matter of the anterior horns of this region of the cord. The brain and cervical cord appeared normal except for slight congestion and hemorrhage; the latter could be readily referred to fracture of the base of the skull. Microscopic examination of the cord, however, revealed little more than that seen in the gross. There were numerous hemorrhages into the gray matter of the lumbar and dorsal cord. Many of the nerve cells in this region stained deeply, but there was no definite cellular infiltration. Six dorsal root ganglia were examined without revealing anything. Pieces of the lumbar cord of this monkey were taken aseptically and preserved in 50 per cent. glycerin.

Dec. 2, 1916, a thick emulsion in physiologic salt solution of the glycerinated cord of Monkey 8 was injected into Monkey 9.

One cubic centimeter was placed in the right lateral ventricle and 6 c.c. in the peritoneal cavity.

Dec. 12, 1916, a thick emulsion in physiologic salt solution of another part of the glycerinated cord of Monkey 8 was injected into Monkey 6 (Monkey 6 had been used six weeks previously in Experiment 1 (d), but had remained perfectly well).

Two cubic centimeters of the emulsion were placed in the left lateral ventricle and 2 c.c. in the peritoneal cavity.

Both of these monkeys remained well up to the time of writing, Jan. 22, 1917.

THE INFLUENCE OF SPLENECTOMY ON METABOLISM IN ANEMIA *

W. DENIS

BOSTON

Although it has long been known that the removal of the spleen can be effected with impunity, comparatively little data is available regarding the relation of this organ to metabolism. A few experiments made on dogs¹ have led essentially to negative results, while in the four cases² in which metabolism studies have been conducted on human subjects, both before and after splenectomy, it was found that more or less definite metabolic changes could be detected after operation.

In the cases studied by Umber, in which splenectomy had been performed on two persons suffering from Banti's disease, this investigator found that after splenectomy it was easier to bring the subjects into nitrogenous equilibrium, a fact which he attributes to the "toxic" action of the spleen in this disease. It was also noted that the output of purins was slightly increased. In one case studied by Minot, a woman suffering from pernicious anemia, it was found that whereas the patient had shown a slight negative nitrogen balance before splenectomy, this changed to a positive balance after operation. This worker also found a slight increase in the percentage of urea nitrogen in the urine after splenectomy.

In a case of congenital hemolytic icterus studied by Goldschmidt and his collaborators, it was observed that a slight positive nitrogen balance before splenectomy was followed by an increased retention after operation; that the output of uric acid showed a decrease of 47 per cent. after operation, and that a large loss of iron through the feces before splenectomy was followed by a decrease of 40 per cent. after operation.

During the past year I have had the opportunity of conducting metabolism experiments before and after removal of the spleen on six patients of this hospital who were operated on for the relief of various types of anemia.³ In all cases the patients were kept in bed during the

* Submitted for publication Feb. 23, 1917.

* From the Chemical Laboratory of the Massachusetts General Hospital.

1. Paton: *Jour. Physiol.*, 1899-1900, **25**, 443. Goldschmidt and Pearce: *Jour. Exper. Med.*, 1915, **22**, 319.

2. Umber: *Ztschr. f. klin. Med.*, 1904, **55**, 289; *ibid.*, München. med. Wehnschr., 1912, **69**, 1478. Minot: *Bull. Johns Hopkins Hosp.*, 1914, **25**, 338. Goldschmidt, Pepper and Pearce: *THE ARCHIVES INT. MED.*, 1915, **16**, 437.

3. These persons were under the care of Drs. Roger I. Lee, George R. Minot, and Beth Vincent, who have not only allowed me to make use of their patients, but have cooperated in every way towards the successful employment of this material for experimental purposes.

periods of observation, and were under the care of a special nurse trained in metabolism work, who had entire charge of the weighing, cooking and serving of food, the collection of excreta and the drawing of blood. Body temperatures were taken by mouth each day, morning and evening. As no deviation from normal appeared in any case, these observations are not recorded in detail in the tables.

In each case a purin- and creatin-free diet was selected, suitable both qualitatively and quantitatively to the taste of the individual patient. This diet was then used in the presplenectomy as well as in the postsplenectomy periods, the subjects being in each case required to eat all food served them. In looking over the diet lists given below it will be noted that in every case these diets, although of high calorific value, were low in protein (50 to 65 gm.). This is due to the fact that all of the patients used were possessed of but little appetite, and on this account it seemed best, if they were to be required to eat the entire ration each day, to make this ration of such a nature that it could be consumed with comfort by the subject. In all cases currents were used as a "marker" to separate the feces passed during the experimental periods.

METHODS EMPLOYED

The analytical methods used were as follows:

For Urine: Total nitrogen, urea, ammonia, Folin-Denis methods.⁴

Uric Acid: In Cases 1 and 2 the Folin-Shaffer method was employed; in the remaining cases the determination was made by an as yet unpublished modification of the colorimetric method of Folin and Denis.

Creatinin and Creatin: Folin's micro methods.⁵

Total Sulphur: Benedict's method (as modified by the author⁶).

Ethereal and Inorganic Sulphates: Folin's methods.⁷

Phosphates: By the uranium acetate titration.

For Feces: Total nitrogen by the Kjeldahl methods.

For Blood: Nonprotein nitrogen, Folin-Denis methods;⁸ total fat, lecithin and cholesterol, Bloor's methods.⁹

DATA CONCERNING CASES

CASE 1.—*Splenectomy for pernicious anemia*.—The first patient studied, Mr. K., 52 years old, was a poorly developed and poorly nourished man weighing only 98 pounds. In this case the disease had probably been in progress for about

4. Folin and Denis: Jour. Biol. Chem., 1916, 26, 473.

5. Folin: Jour. Biol. Chem., 1914, 17, 475.

6. Denis: Jour. Biol. Chem., 1910, 8, 401.

7. Folin: Jour. Biol. Chem., 1905, 1, 131.

8. Folin and Denis: Jour. Biol. Chem., 1916, 26, 491.

9. Bloor: Jour. Biol. Chem., 1915, 23, 317; *ibid.*, 1916, 24, 227 and 450.

one year. The data concerning the past history, physical examination, etc., will not be given here as they offered nothing of interest in connection with this work.

Blood examination made on the first day of observation during the pre-splenectomy period showed:

Red cells	1,200,000
White cells	3,000
Hemoglobin (Sahli)	35 per cent.

The patient was splenectomized, March 1, by Dr. Beth Vincent. He made a rapid and uneventful recovery, and twenty-six days after the operation a second period of observation was begun.

Blood examination made of the first day of this period showed:

Red cells	2,500,000
White cells	7,100
Hemoglobin	80 per cent.

The food served was the same each day and consisted of the following:

	Gm. or c.c.
Oranges (selected to weigh 150 gm.).....	4
Eggs (selected to weigh 50 gm.).....	3
Oatmeal	37
Bread	120
Sugar	80
Potato	150
Peas (canned)	100
Butter	80
Cream (40 per cent. fat).....	250
Milk (3.5 per cent. fat).....	350

Mr. K. consumed the above diet for six days before splenectomy. The excreta passed during the first two days of this period were discarded, only that secured during the last five days being analyzed. Twenty-five days after splenectomy another experimental period of six days was begun, and here, as before, only the excreta passed during the last five days of the period were analyzed.

CASE 2.—*Splenectomy for pernicious anemia.*—The second patient, Mr. B., was 28 years old and weighed 120 pounds. His illness had been in progress about thirteen months. His family history, past history, and the results of the physical examination present nothing of interest in connection with the work described in this paper, and will therefore be omitted.

Blood examination made on the first day of the presplenectomy period showed:

Red cells	824,000
White cells	2,000
Hemoglobin	38 per cent.

Splenectomy was performed, May 15, by Dr. Beth Vincent. Recovery was rapid and May 28, thirteen days after operation, a second series of metabolism observations was begun. At this time an examination of the blood gave the following results:

Red cells	2,100,000
White cells	8,000
Hemoglobin	60 per cent.

The daily ration served to this patient during both the presplenectomy and postsplenectomy periods was as follows:

	Gm. or c.c.
Grape fruit	100
Orange	150
Cream of wheat.....	25
Bread	150
Crackers	25
Butter	60
Eggs (selected to weigh 50 gm. gross).....	3
Cream (40 per cent. fat).....	250
Whole milk (3.5 per cent. fat).....	250
Sugar	80
Potato	100
Onions	100
Tomato	100
Lettuce	40

Mr. B. consumed the above diet for seven days before splenectomy, and for a like period after the operation. In both cases the excreta collected on the first two days of the experimental period were discarded, only the excreta passed on the last five days being analyzed.

CASE 3.—*Splenectomy for Banti's disease*.—The third patient, Miss C., was 17 years old and weighed 86 pounds.

The patient knew nothing of her parents, but stated that she had always been yellow since an attack of jaundice in early childhood, the exact date of which she was unable to recall. At the time of entering the hospital her skin was markedly pigmented, the sclera being also slightly icteroid.

Physical examination showed nothing of interest except a mass on the right side of the abdomen which was felt $6\frac{1}{2}$ cm. from the midsternal line, and which protruded from under the right costal border. This mass was considered by the medical and surgical consultants to be an enlarged spleen.

Blood examination made on the first day of the presplenectomy period showed:

Red Cells	2,292,000
White cells	8,100
Hemoglobin	55 per cent.

The spleen, which weighed 611 gm., was removed, May 31, by Dr. Beth Vincent. The patient made an uneventful recovery and on June 14 a second series of observations was begun. At this time blood examination gave the following results:

Red cells	4,200,000
White cells	126,000
Hemoglobin	110 per cent.

The changes produced by splenectomy on the physical characteristics of the urine in this case were very striking. Before operation the urine was invariably of the deep mahogany brown color characteristic of hemolytic jaundice. In the urine passed as early as twenty-five hours after operation this color had markedly diminished, and in that passed three days after splenectomy it had entirely disappeared.

The daily ration taken by Patient 3 was as follows:

	Gm. or c.c.
Milk (3.5 per cent. fat).....	250
Cream (40 per cent. fat).....	180
Butter	60
Egg (selected to weigh 50 gm. gross).....	1
Sugar	40

	Gm. or c.c.
Bread	225
Orange	100
Potato	100
Carrots	100
Asparagus	100
Lettuce	40
Turnips	100
Cocoa (powder)	8
Oatmeal	25

CASE 4.—*Splenectomy for hereditary jaundice.*—The fourth patient, Mr. W., was 29 years old and weighed 118 pounds. Aside from chronic jaundice, from which he had suffered since early childhood, the patient had always been well until about six months before entrance into the hospital. Physical examination showed a well developed but poorly nourished young man, with skin and sclera both distinctly yellow. The spleen was barely palpable.

Blood examination made on the first day of the presplenectomy observation period gave the following results:

Red cells	3,882,000
White cells	15,550
Hemoglobin (Sahli)	101 per cent.

Splenectomy was performed, July 1, by Dr. Beth Vincent. Recovery was rapid, and ten days later a second series of observations was made.

Blood examination made at this time showed:

Red cells	4,568,000
White cells	20,400
Hemoglobin (Sahli)	106 per cent.

The daily ration taken by this patient consisted of the following:

	Gm. or c.c.
Grape fruit	150
Pineapple	100
Cornmeal	25
Bread	150
Potato	250
Butter	40
Milk (3.5 per cent. fat)	100
Cream (40 per cent. fat)	360
Eggs (selected to weigh 50 gm. gross)	3
Gelatin	50
Cocoa	8
Sugar	80
Lettuce	65
Asparagus	100

CASE 5.—*Splenectomy for "Atypical splenic anemia."*—The fifth patient, Mrs. L., 38 years old, and weighing 139 pounds, had been suffering for about one year with an abdominal tumor which had increased in size steadily and progressively. This tumor was believed by the surgical and medical consultants to be an enlarged spleen, and splenectomy was advised.

Blood examination made on the first day of the presplenectomy period showed:

Red cells	4,620,000
White cells	17,000
Hemoglobin (Sahli)	85 per cent.

November 10, splenectomy was performed by Dr. Beth Vincent. The following description of the spleen is taken from the report of the pathologist (Dr. Hartwell).

"A large thick spleen weighing 140 gm. Microscopic examination gives the appearance of a richly cellular tumor with a reactionary fibrosis. The cells are similar to those of the bone marrow, namely, various forms of myelocytes, nucleated red, and large multinucleated cells suggesting megakaryocytes. The histologic structure is similar to that seen in myelogenous leukemia."

Recovery after operation was rapid, and as the patient was anxious to return home as promptly as possible, a second period of observation was begun seven days after splenectomy.

The daily ration served this patient was as follows:

	Gm. or c.c.
Oranges (selected to weigh 150 gm. gross).....	2
Grape fruit (selected to weigh 200 gm. gross).....	1
Eggs (selected to weigh 50 gm. gross).....	2
Shredded wheat	25
Oatmeal	37
Bread	125
Potato	150
Lettuce	25
Tomato	100
Butter	80
Milk (3.5 per cent. fat).....	300
Cream (40 per cent. fat).....	200
Sugar	50

CASE 6.—*Splenectomy for Banti's Disease.*—The sixth patient, Mr. C., 46 years old, weighed 139 pounds. For the previous year the patient had been suffering from pain in his back, legs and feet, and for the previous six months his abdomen had been increasing in size, and he had been troubled with a feeling of weakness which had made it necessary for him to abandon his work as an operative in a shoe factory.

Blood examination made on the first day of the experimental period gave the following results:

Red cells.....	2,688,000
White cells	4,200
Hemoglobin	54 per cent.

Splenectomy was performed, November 28, by Dr. Beth Vincent, the spleen weighing 1,640 gm. Recovery was rapid, and seven days later a second period of observation was commenced.

The daily ration served to this patient was as follows:

	Gm. or c.c.
Banana	150
Orange	100
Eggs (selected to weigh 50 gm gross).....	3
Bread	125
Potato	75
Peas (canned)	50
Corn (canned)	50
Butter	60
Milk (3.5 per cent. fat).....	500
Cream (40 per cent. fat).....	250
Sugar	50

TABLE 1.—CASE 1 (PERNICIOUS ANEMIA)

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Creat- inin, Gm.	Crea- tin, Gm.	Uric Acid, Gm.	Total Phos- phates as P ₂ O ₅ , Gm.	Feces
Before Splenectomy									
2/21-22	44.5	1,222	5.98	0.36	0.71	0	0.21	1.22	Mixed feces for 4 days, dry wt., 285 gm.; nitro- gen, 10.62 gm.
2/22-23	980	4.90	0.29	0.72	0	0.18	1.03	
2/23-24	940	5.63	0.35	0.70	0	0.18	0.80	
2/24-25	940	4.48	0.30	0.72	0	0.18	0.72	
			20.99	1.30	2.84	0	0.75	3.77	
After Splenectomy									
3/28-29	45.8	800	6.80	0.35	0.68	0	0.26	1.24	Mixed feces for 4 days, dry wt., 99.8 gm.; nitro- gen, 5.12 gm.
3/29-30	820	6.18	0.38	0.73	0	0.28	1.46	
3/30-31	920	6.49	0.36	0.68	0	0.24	1.75	
3/31-4/1	960	6.69	0.38	0.72	0	0.26	2.09	
			26.16	1.47	2.81	0	1.04	6.44	

TABLE 2.—CASE 2 (PERNICIOUS ANEMIA)

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Creat- inin, Gm.	Crea- tin, Gm.	Uric Acid, Gm.	Total Phos- phates as P ₂ O ₅ , Gm.	Feces
Before Splenectomy									
5/ 8- 9	54.5	880	7.70	0.27	1.00	0	0.59	0.97	Mixed feces for 5 days, dry wt., 81.0 gm.; nitro- gen, 4.07 gm.
5/ 9-10	1,240	8.30	0.31	0.99	0	0.63	1.58	
5/10-11	1,250	8.35	0.38	1.08	0	0.60	1.21	
5/11-12	1,020	6.12	0.29	1.06	0	0.57	1.08	
5/12-13	1,000	5.75	0.28	1.05	0	0.55	1.09	
			36.22	1.53	5.18	0	2.94	5.93	
After Splenectomy									
5/31-6/1	52.2	1,000	5.55	0.42	1.05	0	0.47	1.09	Mixed feces for 5 days, dry wt., 135 gm.; nitro- gen, 5.55 gm.
6/1-2	1,400	6.79	0.45	1.08	0	0.54	1.41	
6/2-3	1,460	7.44	0.47	1.08	0	0.54	1.23	
6/3-4	1,220	5.61	0.40	1.00	0	0.54	1.42	
6/4-5	1,360	6.60	0.46	0.99	0	0.53	0.95	
			31.99	2.20	5.20	0	2.62	6.10	

TABLE 3.—CASE 3 (BANTI'S DISEASE)

Date	Wt. Kg	Vol. of Urine, C.c.	Total Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Creat- inin, Gm.	Crea- tin, Gm.	Uric Acid, Gm.	Total Phos- phates as P ₂ O ₅ , Gm.	Feces
Before Splenectomy									
5/26-27	39.0	700	4.65	0.44	0.58	0.19	0.60	0.83	Dry weight of mixed stools for five days, 108 gm.; nitro- gen, 5.77 gm.
5/27-28	700	4.06	0.40	0.56	0.09	0.49	0.61	
5/28-29	560	3.93	0.37	0.59	0.14	0.47	0.60	
5/29-30	1,020	4.13	0.40	0.58	0.10	0.50	0.73	
5/30-31	680	3.30	0.37	0.58	0.05	0.50	0.77	
			20.07	1.93	2.89	0.57	2.46	3.54	
After Splenectomy									
6/16-17	33.6	980	5.09	0.33	0.50	0.07	0.38	0.51	Dry weight of mixed stools for five days, 90 gm.; nitro- gen, 5.10 gm.
6/17-18	850	4.20	0.42	0.46	0.17	0.36	0.75	
6/18-19	1,020	5.35	0.37	0.48	0.11	0.39	0.95	
6/19-20	530	4.00	0.39	0.47	0.08	0.36	0.85	
6/20-21	700	3.90	0.39	0.48	0.09	0.31	0.82	
			22.54	1.90	2.39	0.52	1.80	3.00	

TABLE 4.—CASE 4 (FAMILY JAUNDICE)

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Creat- inin, Gm.	Crea- tin, Gm.	Uric Acid, Gm.	Total Phos- phates as P ₂ O ₅ , Gm.	Feces
Before Splenectomy									
6/24-25	53.6	840	10.90	0.40	1.20	0.14	0.41	1.24	Total dry weight of mixed feces for five days, 80.0 gm.; nitro- gen, 4.35 gm.
6/25-26	1,520	9.74	0.47	1.26	0.38	0.48	1.06	
6/26-27	2,200	7.55	0.57	1.27	0.05	0.45	1.22	
6/27-28	1,400	9.99	0.52	1.28	0.30	0.49	1.96	
6/28-29	1,200	10.89	0.39	1.30	0.00	0.40	1.40	
			49.07	2.35	6.31	0.87	2.23	6.88	
After Splenectomy									
7/11-12	50.0	1,160	10.33	0.24	1.22	0.06	0.50	1.92	Total dry weight of mixed feces for five days, 79.0 gm.; nitro- gen, 3.95 gm.
7/12-13	1,140	9.77	0.29	1.21	0.21	0.44	1.86	
7/13-14	770	9.33	0.28	1.19	0.00	0.38	2.02	
7/14-15	850	9.37	0.21	1.15	0.00	0.38	2.37	
7/15-16	1,140	11.10	0.34	1.17	0.00	0.45	1.48	
			49.90	1.33	5.94	0.27	2.15	9.65	

TABLE 5.—CASE 5 ("ATYPICAL SPLENIC ANEMIA")

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Creat- inin, Gm.	Crea- tin, Gm.	Uric Acid, Gm.	Total Phos- phates as P ₂ O ₅ , Gm.	Feces
Before Splencetomy 11/1-2	6.31	380	4.42	0.35	0.84	0.13	0.42	0.97	Dry weight of mixed feces for four days, 125 gm.; nitrogen, 6.76 gm.
11/2-3	470	4.80	0.35	0.78	0.36	0.42	0.88	
11/3-4	460	3.89	0.38	0.79	0.45	0.44	0.80	
11/4-5	1,160	4.46	0.46	0.94	0.12	0.42	0.81	
			17.57	1.54	3.35	1.06	1.70	3.46	
After Splencetomy 11/19-20	400	5.80	0.41	0.85	0.10	0.56	0.80	Dry weight of mixed feces for four days, 109 gm.; nitrogen, 5.28 gm.
11/20-21	510	5.75	0.50	0.86	0.11	0.53	0.96	
11/21-22	560	5.95	0.54	0.91	0.33	0.56	1.00	
11/22-23	850	5.60	0.45	0.84	0.24	0.60	1.07	
			23.10	1.90	3.46	0.78	2.25	3.83	

TABLE 6.—CASE 6 (BANTI'S DISEASE)

Date	Wt. Kg.	Vol. of Urine, C.c.	Total Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Creat- inin, Gm.	Crea- tin, Gm.	Uric Acid, Gm.	Total Phos- phates as P ₂ O ₅ , Gm.	Feces
				Gm.				Gm.	
Before Spleneetomy 11/21-22	63.1	820	8.05	0.57	1.10	0	0.53	1.10	Dry weight of mixed feces for four days, 62 gm.; nitrogen, 2.9 gm.
11/22-23	820	6.76	0.46	0.97	0	0.55	1.14	
11/23-24	780	6.12	0.52	0.91	0	0.59	0.94	
11/24-25	870	6.44	0.66	0.98	0	0.53	0.72	
			27.37	2.21	3.96	0	2.25	3.90	
After Spleneetomy 12/6-7	61.0	1,390	7.39	0.35	0.98	0	0.61	1.39	Dry weight of mixed feces for four days, 69 gm.; nitrogen, 3.2 gm.
12/7-8	1,000	7.15	0.58	0.86	0	0.51	1.15	
12/8-9	1,800	7.92	0.47	0.99	0	0.55	1.09	
12/9-10	1,560	7.61	0.42	0.94	0	0.57	1.12	
			30.07	2.02	3.77	0	2.24	4.75	

INFLUENCE OF SPLENECTOMY ON NITROGENOUS METABOLISM

1. *Total Nitrogen of Urine and Feces*.—No attempt was made in any case to obtain nitrogen balances, as it was felt that the time during which the patients could be detained for experimental purposes (about ten days) was insufficient to give reliable results from such work.

In general, no characteristic or constant effect which could be directly attributed to the removal of the spleen was found in the study of nitrogen excretion. It is not without interest to note, however, that in four of the six cases studied, the urinary nitrogen was distinctly increased during the postsplenectomy period, and that this increase in urinary nitrogen was accompanied by a corresponding decrease in the fecal nitrogen.

2. *Ammonia*.—In four cases no appreciable difference in the ammonia excretion was found in the two periods; in Case 2 (pernicious anemia) the ammonia in the second period is considerably higher than in the first (2.20 as against 1.52 gm.), while in Case 4 (family jaundice) the opposite result was obtained.

3. *Creatinin and Creatin*.—No change in the creatinin excretions was noted after operation in any case.

Creatin was absent from the urine in Cases 1, 2 and 6; it was present in the urines in Cases 3, 4 and 5, both before and after operation.

4. *Uric Acid*.—In three cases (2, 4 and 6) the uric acid figures obtained before splenectomy were practically the same as those found after operation. In two cases (1 and 5) there was a marked increase in the uric acid output after splenectomy, while in one case (3) the quantity of uric acid excreted in the second period was much lower than that found in the first.

5. *Phosphates*.—In five cases there was an increase in phosphate excretion in the postoperative period, which, while small in some cases (2), was very considerable in others (1 and 4), while in one case (3) a slight decrease was found. No parallelism, however, was apparent between this increased phosphate excretion and the output of total nitrogen or of uric acid.

INFLUENCE OF SPLENECTOMY ON THE SULPHUR METABOLISM

The sulphur partition was studied in two cases of pernicious anemia (Cases 1 and 2), one of Banti's disease (Case 3), and one of family jaundice (Case 4).

In all four the results obtained are similar. The partition of sulphur between inorganic sulphates, ethereal sulphates and neutral sulphur is essentially normal; no change occurred either in the distribution or in the absolute amounts of the fractions after splenectomy,

except in Case 1, in which it will be noted that the ethereal sulphates are reduced in amount in the post splenectomy period, a phenomenon which is explained by the fact that whereas during the preoperative period the patient was constipated, so that the bowels moved only by means of enemata (given every forty-eight hours), in the postoperative period two to three spontaneous movements occurred each day.

TABLE 7.—CASE 1 (PERNICIOUS ANEMIA) SULPHUR METABOLISM

Date	Total Sulphur as SO ₃ , Gm.	Inorganic Sulphates as SO ₃ , Gm.	Ethereal Sulphates as SO ₃ , Gm.	Neutral Sulphur as SO ₂ , Gm.	Per Cent. of Total Sulphur		
					Inorganic Sulphates	Ethereal Sulphates	Neutral Sulphur
Before Splenectomy							
2/21-22	1.09	0.70	0.14	0.24	64.51	12.95	22.54
2/22-23	1.26	0.91	0.17	0.18	71.94	13.19	14.87
2/23-24	1.14	0.75	0.20	0.19	65.79	17.14	17.06
2/24-25	1.02	0.70	0.10	0.21	69.25	9.41	21.34
After Splenectomy							
3/28-29	1.30	1.04	0.02	0.24	79.62	1.81	18.42
3/29-30	1.25	0.90	0.09	0.26	72.03	6.92	21.05
3/30-31	1.14	0.92	0.05	0.16	80.19	4.46	15.05
3/31-4/1	1.05	0.77	0.09	0.23	73.18	8.52	18.30

TABLE 8.—CASE 2 (PERNICIOUS ANEMIA) SULPHUR METABOLISM

Date	Total Sulphur as SO ₃ , Gm.	Inorganic Sulphates as SO ₃ , Gm.	Ethereal Sulphates as SO ₃ , Gm.	Neutral Sulphur as SO ₂ , Gm.	Per Cent. of Total Sulphur		
					Inorganic Sulphates	Ethereal Sulphates	Neutral Sulphur
Before Splenectomy							
5/ 8- 9	1.53	1.17	0.11	0.25	77.17	7.11	15.72
5/ 9-10	1.78	1.31	0.07	0.40	77.21	3.71	19.08
5/10-11	1.42	1.07	0.12	0.23	75.35	8.45	16.20
5/11-12	1.17	0.86	0.08	0.23	73.56	6.59	19.81
5/12-13	1.23	0.73	0.14	0.36	70.61	11.38	18.01
After Splenectomy							
5/31-6/1	1.40	0.89	0.10	0.40	64.00	7.43	28.57
6/1-2	1.21	0.84	0.12	0.24	69.44	9.99	20.57
6/2-3	1.53	1.03	0.14	0.36	67.55	7.54	24.91
6/3-4	0.97	0.73	0.09	0.15	75.16	8.75	18.09
6/4-5	1.36	1.00	0.10	0.25	73.23	7.46	19.31

TABLE 9.—CASE 3 (BANTI'S DISEASE) SULPHUR METABOLISM

Date	Total Sulphur as SO ₃ , Gm.	Inorganic Sulphates as SO ₃ , Gm.	Etheral Sulphates as SO ₃ , Gm.	Neutral Sulphur as SO ₂ , Gm.	Per Cent. of Total Sulphur		
					Inorganic Sulphates	Etheral Sulphates	Neutral Sulphur
Before Splenectomy							
5/26-27	1.29	0.87	0.16	0.25	77.27	12.39	15.34
5/27-28	1.05	0.73	0.12	0.20	81.11	13.40	18.84
5/28-29	1.14	0.75	1.10	0.20	65.90	8.93	18.12
5/29-30	0.98	0.61	0.15	0.21	62.78	15.71	21.51
5/30-31	0.69	0.43	0.10	0.14	64.35	15.02	20.65
After Splenectomy							
6/16-17	1.16	0.79	0.13	0.23	63.51	11.40	20.09
6/17-18	1.24	0.70	0.27	0.26	56.43	22.46	21.08
6/18-19	1.03	0.65	0.15	0.22	63.01	14.65	22.34
6/19-20	1.11	0.63	0.15	0.28	60.86	13.75	25.39
6/20-21	0.85	0.54	0.13	0.16	61.19	15.93	22.88

TABLE 10.—CASE 4 (FAMILY JAUNDICE) SULPHUR METABOLISM

Date	Total Sulphur as SO ₃ , Gm.	Inorganic Sulphates as SO ₃ , Gm.	Etheral Sulphates as SO ₃ , Gm.	Neutral Sulphur as SO ₂ , Gm.	Per Cent. of Total Sulphur		
					Inorganic Sulphates	Etheral Sulphates	Neutral Sulphur
Before Splenectomy							
6/24-25	1.93	1.44	0.10	0.39	74.01	5.08	20.91
6/25-26	1.78	1.24	0.18	0.35	69.62	10.53	19.80
6/26-27	1.53	1.07	0.14	0.31	70.11	9.18	20.61
6/27-28	2.22	1.53	0.24	0.39	71.23	10.92	17.85
6/28-29	1.84	1.30	0.18	0.36	70.92	9.67	19.41
After Splenectomy							
7/11-12	1.85	1.44	0.19	0.22	77.09	10.71	12.20
7/12-13	1.82	1.39	0.11	0.30	75.99	6.49	17.52
7/13-14	1.64	1.31	0.08	0.25	79.78	4.56	15.56
7/14-15	1.56	1.04	0.24	0.28	67.02	15.96	17.02
7/15-16	1.77	1.23	0.13	0.33	72.67	8.07	19.26

INFLUENCE OF SPLENECTOMY ON THE BLOOD

In view of the great importance which has recently been assigned to the spleen in connection with fat and lipid metabolism by King, by Eppinger and by Medak,¹⁰ it has seemed desirable to make analyses

10. King, J. H.: Studies in the Pathology of the Spleen, THE ARCHIVES INT. MED., 1914, 14, 145. Eppinger: Medak: Biochem. Ztschr., 1914, 59, 419.

of the blood lipoids of these patients both before and after operation. The microchemical methods recently introduced by Bloor make it possible to determine the more important lipoids (fats, lecithin and cholesterol) in the comparatively small amounts of blood which it was considered permissible to take from these patients. Determinations of nonprotein nitrogen have also been made, but on account of lack of material it was necessary to omit determinations of the other blood constituents, such as uric acid, creatinin, etc.

The results presented in Table 11 show that in the five cases in which blood analyses were made, practically no change in the non-protein nitrogen or total fatty acids of the blood was observed, except

TABLE 11.—CHEMICAL EXAMINATION OF BLOOD BEFORE AND AFTER SPLENECTOMY *

		Non-protein Nitrogen, Mg. per 100 Gm. Blood	Corpuscles, per Cent.	Total Fatty Acids, per Cent.		Lecithin, per Cent.		Cholesterol, per Cent.	
				Whole Blood	Plasma	Whole Blood	Plasma	Whole Blood	Plasma
Case 1	Before.....	35	22	0.32	0.27	0.25	0.16	0.13	0.11
	After.....	34	26	0.31	0.24	0.28	0.16	0.21	0.20
Case 2	Before.....	23	14	0.35	0.35	0.16	0.16	0.15	0.15
	After.....	25	17	0.38	0.30	0.21	0.17	0.13	0.13
Case 4	Before.....	51	..	0.24	0.15	0.15	
	After.....	30	31	0.34	0.30	0.18	0.15	0.18	0.16
Case 5	Before.....	..	37	0.46	0.49	0.24	0.20	0.16	0.14
	After.....	..	34	0.47	0.44	0.32	0.22	0.19	0.19
Case 6	Before.....	..	29	0.68	0.55	0.28	0.16	0.16	0.14
	After.....	..	30	0.62	0.54	0.31	0.22	0.17	0.15

* I am indebted to Dr. W. R. Bloor for the determinations of the blood lipoids.

in Case 4, in which the fatty acid figure obtained after splenectomy was considerably higher than that found in the blood sample taken before operation. Lecithin was slightly increased in the whole blood, and also showed somewhat higher values in the plasma in Cases 5 and 6. Cholesterol was increased in both whole blood and plasma except in Case 2, in which a slight decrease was found. On the whole, the results obtained do not confirm the results of Eppinger and of King regarding the increased content of fat after splenectomy. They are, however, in accordance with the statements of these authors concerning the increased blood cholesterol found after splenectomy.

SUMMARY

Metabolism studies have been conducted before and after operation in six cases of anemia in which splenectomy was performed. These included two cases of pernicious anemia, two of Banti's disease, one of family jaundice and one of "atypical splenic anemia."

It was found that while, in some of the cases examined, changes in the excretion of certain bodies occurred, these changes were not constant; thus in two cases the uric acid output was much increased after operation, in one it was reduced, while in three no change was noted.

In a series of observations on the phosphate excretion it was found that while in five cases the output of phosphates by the kidney was increased after operation, in one (Case 3) it was decreased.

It is of interest to note that there is no relation between these changes in uric acid and phosphate excretion and the increase in leukocytes noted in the blood counts made during the postoperative period. Thus in Case 3, 8,100 white blood cells were present during the first period and 126,000 during the second, whereas there is a decrease in the excretion of phosphates and uric acid. In Case 1, however, the white blood cells increased only from 3,000 to 7,100, while the uric acid and phosphate excretion was almost doubled.

A study of the sulphur excretion showed no changes, either relative or absolute, which could in any way be attributed to the removal of the spleen.

Blood analyses did not confirm the findings of King and Eppinger regarding the increased content of fat in the blood after splenectomy; cholesterol was found to be more or less increased in every case. I have noted in several cases, however, that in anemia the low blood cholesterol figures so commonly found in this disease almost invariably increase noticeably when the blood picture is improved, whether this be accomplished by transfusion or by spontaneous remission.

Massachusetts General Hospital.

THE ELECTROCARDIOGRAM; ITS RELATION TO CARDIODYNAMIC EVENTS *

CARL J. WIGGERS, M.D.
NEW YORK

I. INTRODUCTION

A clearer conception of the temporal relation that each variation of the electrocardiogram bears to systole and diastole of the auricles and ventricles is of twofold importance. It is essential, if the electrocardiogram is to be utilized, directly or indirectly, as a diagnostic criterion of the functional capacity of the heart. It is indispensable in explaining the ultimate cause of the electrocardiogram variations, for obviously no dynamic process can be held responsible for any electrical variation with which it is not isochronous.

In discussing the time relations it is important to be oriented as to the precise events that merit comparison. It is quite generally recognized that the electrical variations recorded in the electrocardiogram by the three customary leads do not occur in an invariable relation to each other or to a definite phase of the cardiac cycle.

Einthoven,¹ in 1908, first directed attention to the fact that *peaks* bearing the same letter occur in different phases of the cardiac cycle. Kahn² found that if the summit of P is used as a standard, then peak R_I precedes peak R_{II} and this in turn comes earlier than peak R_{III}. In transcribed curves published by Fahr³ and Einthoven, Fahr and Waart⁴ peaks R_{II} and R_{III} are synchronous, but later than peak R_I. These differences are not only relative to other waves, but real, as shown by simultaneous leads taken during identical heart cycles. In carefully measured curves Williams⁵ found the relations variable and not to be predicted. In three cases R_I was delayed (0.006 second); in two cases R_I and R_{II} were in phase and preceded by R_{III}; in one case all peaks were in phase.

The phase difference of the summit of the P wave is even greater. In one case Williams⁵ found the summit of P_I to be 0.02 second later than the summits of P_{II} and P_{III}. Differences as great as 0.04 second are shown in the curves published by Fahr³ and Einthoven, Fahr and Waart.⁴ Uniformly the summit of P_I seems to be delayed.

The initial rise of the P and R waves is quite variable in different leads. In the case of the P wave this is due in part to the difficulty of determining exactly the initial rise. In the case of the R wave, the presence of a Q depression in one lead and its absence in another often complicate the question. Hoffmann⁶ concluded that the rises of R_I and R_{II} occur simultaneously, but

* Submitted for publication Feb. 19, 1917.

* From the Physiological Laboratory of Cornell University Medical College.

1. Einthoven: Arch. f. d. ges. Physiol., 1908, **122**, 588.

2. Kahn: Arch. f. d. ges. Physiol., 1909, **129**, 291; Ergebn. d. Physiol., 1914, **14**, 69.

3. Fahr: Heart, 1912-1913, **4**, 147.

4. Einthoven, Fahr and Waart: Arch. f. d. ges. Physiol., 1913, **150**, 275.

5. Williams: Am. Jour. Physiol., 1914, **35**, 295.

6. Hoffmann: Zentralbl. f. Herz. u. Gefässkrankh., 1912, **4**, 187.

that the rise of R_{III} is delayed. According to Kahn,² the beginnings of Q_I, Q_{II} and Q_{III} are progressively delayed when compared with the summit of P. According to one of the plotted curves of Fahr,³ the rise of R_{II} and R_{III} are synchronous, while the rise of R_I is delayed; in another curve the initial deflection of R coincides in Leads I and III but is delayed in Lead II. In simultaneous leads published by Williams, R_I and R_{II} begin synchronously, but the rise of R_{III} is delayed fully 0.01 second.

The necessity of selecting a *standard lead* for all time comparisons with dynamic events is evident. For this purpose Lead II has been almost universally used, not only because the waves are larger and more certain in the direction of the deflections, but also because their relation to the electrical negativity of different regions of the heart has been experimentally established (see accompanying figure). By comparing with an auricular myogram, first the electrical variations of Lead II and then the time of initial negativity at the sinus node, Eyster and Meek⁷ found that the rise of P_{II} begins approximately 0.01 second after initial negativity of the sinus node appears. By simultaneously recording the electrocardiogram by Lead II and the initial negativity of the exposed heart, Lewis, Meakins and White⁸ were able to confirm this relation. They further showed that within 0.03 second the wave of negativity had reached the right auricular appendage and within 0.045 second the ear of the left auricle. It is interesting to note that this corresponds practically to the summit of P_{II} (see figure).

The earliest evidence of negativity in the ventricle, according to Lewis and Rothschild,⁹ occurs 0.01 to 0.015 second before the upstroke of R_{II}, or about 0.005 second before the Q_{II} depression when present. The "central region" of the right ventricle is negative, almost simultaneous with the onset of R_{II}. According to Erfmann,¹⁰ the entire ventricular surface then becomes negative within a few thousandths of a second, but the more detailed investigations of Lewis and Rothschild⁹ show that at least 0.02 to 0.03 second is required before the negative wave has spread over the entire ventricular surface. This point coincides approximately with the summit of R_{II}.

II. RELATION OF THE ELECTRICAL VARIATIONS TO AURICULAR SYSTOLE

Inasmuch as the P-R interval approximately corresponds to the period assigned to auricular systole by Marey,¹¹ Einthoven and de Lint¹² at first attributed both the P elevation and Q depression to

7. Eyster and Meek: *THE ARCHIVES INT. MED.*, 1913, **11**, 233.

8. Lewis, Meakins and White: *Phil. Tr. Roy. Soc. London*, 1914-1915, B, **205**, 381.

9. Lewis and Rothschild: *Phil. Tr. Roy. Soc. London*, 1914-1915, B, **206**, 219.

10. Erfmann: *Ztschr. f. Biol.*, 1913, **61**, 155.

11. Marey: *La circulation du sang*, 1881, p. 96.

12. Einthoven and de Lint: *Arch. f. d. ges. Physiol.*, 1900, **80**, 139.

auricular systole. Later, on finding that the Q depression always precedes R rather than follows P when the auricular contraction does not occupy a presystolic position, Einthoven¹³ concluded that the Q depression is due to ventricular systole.

Many attempts have since been made to establish more precisely the relation of the P wave to auricular systole. We may pass at once to a review of the experimental work, since the efforts to establish the relation to auricular systole in man by the aid of the venous pulse and apex cardiograms have been and must continue to be futile. Neither gives any precise information regarding the onset of auricular contraction.

Relation to the Onset of Auricular Contraction.—In experimental animals the electrocardiogram waves have frequently been related to the onset of the mechanical contraction curve recorded by attaching a light lever, through a string, with an auricular appendage. The comparison of the electrical variations with such a "suspension curve" simultaneously recorded, indicates that the mechanical contraction not only occurs later than the rise of the P wave, but that it does not even begin until the P wave has been practically completed. As examples, we may consider the results of Kahn,¹⁴ showing a delay of 0.04 to 0.05 second, and those of Eyster and Meek,⁷ showing a delay of 0.07 second in the mechanical response.

Such results readily lead to the conclusion that the P wave is not associated with auricular contraction, but rather with the conduction of impulses across the auricles. Before such an assumption may be made it is clearly necessary to satisfy ourselves that the methods employed to determine the onset of systole equal in their sensitiveness and accuracy the method used to detect variations in electrical potential. In a recent series of papers¹⁵ dealing with the physiology of the mammalian auricle, reasons were given to show why the "suspension curve" of the auricle cannot be trusted to indicate even the onset of auricular systole correctly. Furthermore, an accurate myogram recorded from two approximating points on the auricular surface also does not show the onset of mechanical contraction. The reasons for this seem to be clear: Not all portions of the auricular muscle are excited simultaneously, but each fractionate portion of muscle is successively excited as the impulse spreads radially from the sinus node to the more distant fractions. A myogram recorded from the anterior auricular surface or appendage, therefore, does not indicate the earliest movement of the auricular muscle near the sinus region. Experiments¹⁵ have shown

13. Einthoven: Arch. internat. de physiol., 1906, **4**, 132.

14. Kahn: Arch. f. d. ges. Physiol., 1910, **132**, 209.

15. Wiggers: Am. Jour. Physiol., 1916, **40**, 218; *ibid.*, **42**, 133 and 141.

that the intra-auricular pressure rises approximately 0.02 second earlier than the deflection of the auricular myogram. The intra-auricular pressure curve evidently gives a very much more accurate indication of the onset of mechanical systole of the auricle.

Using this as a standard of comparison, Kahn¹⁶ obtained very variable relations. Lewis¹⁷ publishes a diagram, apparently based on uncited experiments, which places the initial rise of intra-auricular pressure 0.04 second after the rise of P_{II}. This work was done before accurate forms of recording manometers were available. The first comprehensive study of this question was carried out by Garten and Weber,¹⁸ who employed an efficient and accurate intra-auricular manometer capable of recording the pressure variations electrically. They found that P_{II} precedes the rise of intra-auricular pressure only 0.013 to 0.021 second. These figures have practically been confirmed in this laboratory¹⁵ where an average delay of 0.022 second was found for the rise of the intra-auricular pressure recorded by an optical manometer. *The onset of auricular systole thus established as beginning about 0.02 second after the rise of P_{II} occurs on the ascending curve or near the summit of P_{II} (see figure).*

Relation to the Phases of Auricular Systole.—Auricular systole is not a simple and united contraction process, but a rapid peristalsis. It has already been pointed out that the excitation wave spreads radially from the sinus node and in its spread excites consecutive portions of the auricle to contract. Receiving its excitation earlier, the auricular tissue near the sinus node begins to contract 0.02 second before the anterior surface of the auricle. Consequently, the anterior portion or body of the auricle does not begin to contract until 0.04 second after the rise of the P_{II} wave; that is, on its descending limb. Not until 0.02 second later, that is, 0.06 second after the rise of P_{II}, is the entire auricle, to judge from the contour of the myogram curve,¹⁵ in a state of contraction. *In short, while the tissue near the sinus node begins to contract 0.02 second after the first rise of P_{II}, the tissue near the right auricular appendage does not begin to contract until P_{II} has been entirely completed (see figure).*

Relation to the End of Auricular Systole.—When once excited, each fractionate portion of the auricular syncytium continues to contract for an interval of about 0.05 second. Consequently, by the time the most distant portions begin to contract, the more proximal portions are nearing the end of their contraction phase. The total interval that all auricular fibers unite in contracting is consequently very short and

16. Kahn: Arch. f. d. ges. Physiol., 1909, 126, 197.

17. Lewis: Mechanism of the Heart Beat, London, 1911, p. 24, fig. 13.

18. Garten and Weber: Ztschr. f. Biol., 1915, 66, 83.

does not exceed 0.015 second. At the end of this time, that is, 0.075 second after the rise of P_{II}, the intra-auricular pressure begins to fall and the myogram curve, though still continuing to indicate shortening of the auricular fibers, changes its contour.¹⁵ These facts have been interpreted to mean that the auricular tissue situated near the sinus node has begun to relax. This relaxation process gradually spreads to the more distal portion, but it requires 0.05 second more before a balance between contracting and relaxing units has been reached so that the mass of auricular tissue neither shortens nor lengthens. *From a dynamic point of view it seems desirable to regard this point, which occurs about 0.105 second after the beginning of auricular systole and 0.125 second after the rise of P_{II}, as the termination of auricular systole.*

The relation that the termination of auricular systole bears to the R_{II} variation is determined largely by the P-R interval; in a certain measure also by a slight variation in the length of auricular systole. Taking the interval 0.105, referred to in the foregoing, as an average duration, it is evident that if the P-R interval equals 0.125 second, then the end of auricular systole coincides with the beginning of R_{II}. If the P-R interval is shorter than 0.125 second, or if the duration of auricular systole is larger by only a few hundredths of a second (both very common in the dog), then auricular systole extends into the time interval occupied by the R variation (see figure). This means that in such cases the entire auricle still continues to shorten after the excitation wave has spread to the ventricle. On the other hand, if the P-R interval in Lead II is longer than 0.125 second (which is common in man), then auricular systole ends before the R variation by an interval equal to the additional lengthening of this interval.

III. RELATION OF ELECTRICAL VARIATIONS TO VENTRICULAR SYSTOLE

The relation that the electrocardiogram waves bear to the dynamic systole of the ventricle has been investigated by many methods. An extensive review of this subject was given by Kahn¹⁹ in 1914. It is proposed here to reconsider the relation to the ventricular myogram, the intraventricular pressure curve and the heart sounds in the light of recent discoveries.

Relation to Onset of Ventricular Systole.—Most of the earlier experimental evidence favors the idea that the R_{II} variation is practically completed before mechanical systole has begun. Kahn¹⁴ registered the movements of a light needle inserted into the right ventricle synchronously with the electrocardiogram. Ventricular systole so indi-

19. Kahn: *Ergebn. d. Physiol.*, 1914, **14**, 69.

cated began 0.031 to 0.035 second after the rise of RII. A similar delay was shown in the myocardiographic records obtained by Lewis.¹⁷ Previously, Kahn¹⁹ had found that the intraventricular pressure registered by Gad's *Wellenschreiber* began to rise 0.065 second after RII. It must be conceded, however, that the mechanical apparatus employed by these investigators did not qualify to present-day standards, hence the possibility remains that the delay is not inherent in the heart, but is of instrumental origin.

The introduction into experimental work, by Frank, of manometers with a high vibration frequency has stimulated a number of investigators in recent years to compare again the electrocardiogram variations with the intraventricular pressure curves. Piper²⁰ was the first to report on these relations, but, as his electrogram was led directly from the heart and had a configuration entirely foreign to a normal electrocardiogram, his results were of little apparent value. The question was reinvestigated by Garten²¹ who used his electrically recording manometer. He found that the intraventricular pressure began to rise 0.17 to 0.21 second after the beginning of RII; that is, on the ascending limb. This point, it will be recalled, approximately coincides with the end of auricular systole in the dog. In reinvestigating this question by the use of an optical cardiac manometer it has been found in this laboratory that the onset of the pressure rise is uniformly somewhat later; that is, 0.03 to 0.045 second after the initial rise of the RII wave, thus placing the onset of mechanical contraction on the descending limb of the RII wave. The cause of these discrepancies has not been ascertained. It is significant, however, that the RII wave precedes by a short interval the first evidence of mechanical activity in the ventricle.

Relation to End of Ventricular Systole.—The ventricular myogram has been used by Kahn and Lewis to determine the end of ventricular systole. The impression gained from such experiments is that the T variation occurs during the ejection period of the heart, and that a state of iso-potential is reestablished before the onset of ventricular diastole. On account of the involved nature, and, as yet, uncertain interpretation, of any myographic tracing from the ventricles, it is difficult to adjudge the value of such observations. Garten²¹ determined the relation of the TII variation to the sudden fall of pressure within the ventricle, and found that a far greater variation exists than in other time relations. Systole, as a rule, terminates 0.034 to 0.048 second after the TII variation; at other times it terminates as much as 0.11 second before the end of T. The end of ventricular systole is not

20. Piper: *Centralbl. f. Physiol.*, 1913, 27, 392.

21. Garten: *Ztschr. f. Biol.*, 1915, 66, 23.

always marked sharply, however, on the intraventricular pressure curves. In general, the sudden fall of intra-aortic pressure, designated as the *incisura* by Frank, offers the most exact indication of the termination of ventricular systole. Garten and Wiggers and Dean²² have established the relation of this event to the T wave. These comparisons agree with the results of Garten in showing the variable relation of the end of systole to the T wave. The significant observation has been made that when the period of systole shortens (for example, after epinephrin), then the T wave becomes broader or remains unaltered, and consequently the end of systole comes appreciably before the T wave has ended. *It is quite evident that the end of ventricular systole cannot be definitely related to any phase of the T wave variations.*

Relation to the Heart Sounds.—By comparing the recorded heart sounds with the variations of the synchronously recorded electrocardiogram, these relations of the onset and termination of ventricular systole have been confirmed in animals and extended to man. Kahn²³ and Bull,²⁴ using Weiss' phonoscope, concluded that the first sound vibrations begin 0.03 to 0.04 second after the rise of R_{II}; that is, toward its end. These early attempts to establish electrical and dynamic relations are robbed of much of their significance by the fact that it yet remains to be demonstrated that true sound vibrations can be recorded by this apparatus. The comparison of the sound waves recorded by the phonocardiographic method of Einthoven has given similar results in the hands of Lewis,²⁵ Fahr³ and Battaerd,²⁶ thus confirming the experimental work which places the beginning of ventricular systole on the descending limb of R_{II}.

The issue has been raised, however, whether the first minor vibrations entering into the composition of the first sound are of sufficient intensity to be transmitted to the chest. Fahr³ found that when special precautions are taken and favorable individuals selected, the main group of vibrations is preceded by one or several "initial vibrations" of small size. If these vibrations constitute the first evidence of ventricular activity, then this dynamic event occurs, according to Fahr, on the ascending limb of R_{II}. This question can be settled only by a direct comparison of the first sound vibrations with the intraventricular pressure curve, which can be accomplished satisfactorily only by recording the fundamental sounds directly from the exposed heart. It has

22. Wiggers and Dean: Am. Jour. Physiol., 1917, **42**, 476.

23. Kahn: Arch. f. d. ges. Physiol., 1909, **129**, 291; *ibid.*, 1910, **133**, 597.

24. Bull: Quart. Jour. Exper. Physiol., 1911, **4**, 289.

25. Lewis: Heart, 1912-1913, **4**, 241.

26. Battaerd: Heart, 1915, **6**, 121.

recently come to my attention that this was attempted by Sinelnikow,²⁷ who found that the first sound vibration so recorded began precisely with the rise of intraventricular pressure. As this work remains in unpublished form, however, we have no knowledge as to whether the initial or main vibrations are referred to as occurring isochronously with the intraventricular pressure rise. Dean and I,²² unaware of this unpublished research, carried on similar experiments in which the relation of the various components of the first sound to other cardiac events was analyzed. A specially constructed sound transmitter, stitched to the heart, was connected to a delicate sound recording capsule. It was found that whenever initial vibrations were present they preceded the rise of intraventricular pressure by 0.018 to 0.025 second. *The main vibrations, however, are synchronous with the first rise of intraventricular pressure and may be used as an indication of the onset of ventricular systole.*

Similarly, the second sound has been related to the fall of intraventricular pressure and to the incisura of the aortic curve. Sinelnikow, according to Garten, found that the first vibration never occurs until the lowest part of the incisura is reached. Our results, however, give evidence that they coincide precisely with the *beginning* of the incisura. *The second sound vibrations may therefore be used to indicate definitely and accurately the end of systole.*

Applying these results to the combined records of the sounds and electrocardiogram in animals and man, we must conclude that *ventricular systole begins about 0.03 to 0.04 second after the rise of RII; that is, on its descending limb, while the end of systole, as indicated in experimental work, bears a variable relation to TII, but usually follows the event (see figure).*

IV. SUMMARY AND CONCLUSIONS

In studying the relation between dynamic events and the electrical changes in the heart, it is important that the apparatus utilized to record the several curves at least approximate each other in efficiency and accuracy. This ideal has been attained by the introduction of various types of photographic apparatus, by means of which the dynamic changes in the circulation may be recorded.

The results of such studies show, it is true, minor variations in the relations of dynamic events to the electrical variations recorded by Lead II. These variations are so small, however, that it is possible and desirable to plot on an electrocardiogram the average relation of

27. Sinelnikow: Unpublished experiments referred to by Garten, Ztschr. f. Biol., 1915, ---

specific phases of mechanical activity in the auricles and ventricles. This has been done in the curve shown in the figure.

It is not desirable, with our present limited fund of detailed knowledge, to predict the full significance of these relations. A few observations are apparent:

1. No single elevation of the electrocardiogram agrees precisely with the beginning or end of any mechanical event in the auricle or ventricle. The P and R waves, respectively, precede by several hun-

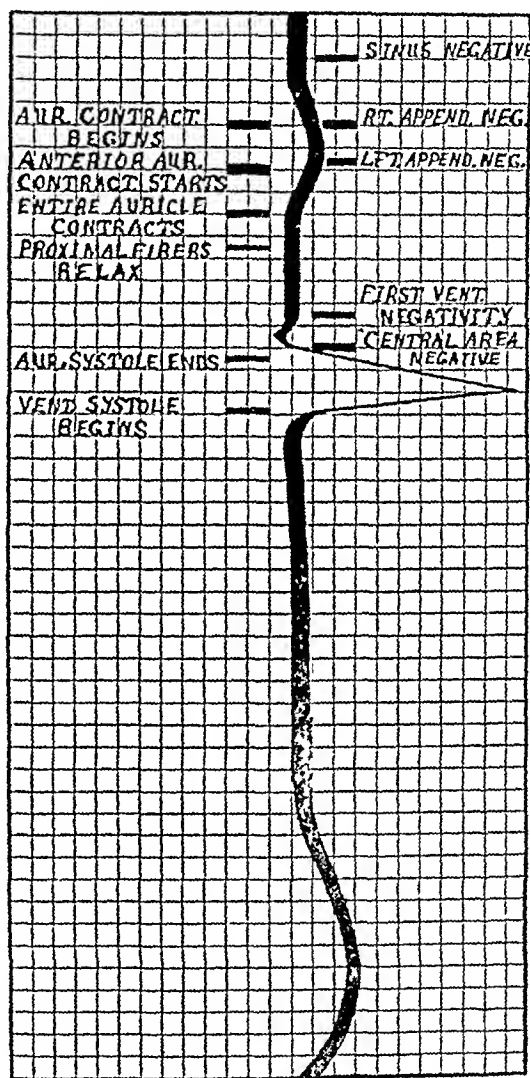


Diagram showing waves of electrocardiogram, Lead II, and their time relations (a) to primary negativity of a few regions of heart and (b) to mechanical changes in auricles and ventricles when P-R interval equals 0.12 second. Abscissae, 1 division = 0.01 second.

dredths of a second the onset of auricular systole and the beginning of ventricular systole. This observation favors the view that these variations are not associated with the contraction process, but with the propagation of the impulse, across the heart.

2. The end of neither auricular nor ventricular systole is definitely marked on the electrocardiogram. Neither the breadth and duration of the P wave nor the P-R interval are related to the duration of auricular systole; nor is the P-T interval at all a criterion of the duration of ventricular systole. This interval may lengthen when the actual duration of systole has decreased. These observations force us to the conclusion that not only is the amplitude of the electrical variations no criterion of the vigor of contraction, as is well recognized, but the time intervals gleaned from an electrocardiogram cannot be used as a guide to the dynamic functions of the heart. Its clinical value remains restricted to questions dealing with abnormal propagation and initiation of impulses and to conditions producing abnormal axes for the heart. In these fields its value is supreme.

477 First Avenue.

STUDIES OF THE BLOOD IN BERIBERI *

SURGEON-INSPECTOR I. YOSHIKAWA†

AND

FLEETSURGEONS K. YANO AND T. NEMOTO

TOKYO, JAPAN

I. REFRACTOMETRIC INVESTIGATION OF THE SERUM

Refractometric investigation of the blood was carried out for the first time by Strubell¹ in 1900. He considered the procedure available for measuring the osmotic pressure of the blood, but Reiss,² after two years' thorough study of the subject (1901-1902), found that the refractive index bears no relation to osmotic pressure, but that refractometric estimation is practically equivalent to a quantitative determination of protein in the blood. To prove that such a relation exists, Reiss cited a table of results of Vaucher,³ in which he compared the figures obtained by refraction with those obtained by weighing the proteins.

According to Reiss, the quantity of nonprotein substances in the blood shows no remarkable variation, although the contrary is generally believed to be true. The freezing point of the blood, for example, is normally 0.56 C., and even in extreme cases it does not fall below 0.49, or exceed 0.71. In the case of uremia, however, he notes that the refraction coefficient is influenced by the accumulation of urea and other substances in the blood, and that consequently the refractometric estimation of proteins is, in uremic cases, not reliable.

Strauss,⁴ in 1904, used the refractometric method, and it has since been taken up by others.⁵ It is now considered by many to be a simple

* Submitted for publication April 2, 1917.

* From the Laboratory of the Naval Medical College, Tokyo.

* Read before the periodical meeting of the Beriberi Research Committee, 1916.

† A member of the Beriberi Research Committee of the Japanese government.

1. Strubell, A.: Ueber refraktometrische Blutuntersuchungen, München. med. Wchnschr., 1902, **49**, 616.

2. Reiss, E.: Die refraktometrische Blutuntersuchung und ihre Ergebnisse f. die Physiologie und Pathologie des Menschen. Ergebn. d. inn. Med., 1913, **10**, 531.

3. Vaucher, E.: L'hydrémie des brightques et des cardiaques oedémateux. Paris, 1911.

4. Strauss, H.: Demonstration der refraktometrischen Blutuntersuchung, Deutsch. med. Wchnschr., 1905, **31**, 83.

5. Neuberg, C.: Der Harn. Berlin, 1911; Tranter, C. L., and Rowe, A. H.: The Refractometric determination of Albumin, Globulin, and Nonprotein in Normal Human Blood Serum, Jour. Am. Med. Assn., 1915, **65**, 1433; Legueu, E.: Nutzen der Anwendung der Harnstoffsekretionskonstante bei den Prostatikern, Berl. klin. Wchnschr., 1913, **50**, 1741.

and convenient method for the estimation of the protein content of the serum.

The present article gives the results of a recent refractometric investigation of the serum of beriberi patients in the Tokyo Municipal Charity Hospital. Abbe's *Universalrefraktometer* was used for the experiments, as Pulfrich's *Eintauchrefraktometer*, which is generally recommended, was not available.

We recognized the desirability of taking the blood at a definite time each day, owing to the influence of the ingestion of food on the protein content, but as all of the patients examined were outpatients, it was

TABLE 1.—VAUCHER'S COMPARISON OF REFRACTOMETRIC AND WEIGHT METHODS OF BLOOD PROTEIN ESTIMATION
HUMAN SERUM

Number or Species	Refraction, per Cent.	Weight, per Cent.
I	8.82	8.79
II	8.5	8.49
III	9.41	9.417
IV	8.11	8.12
V	9.2	8.192
ANIMAL SERUM		
Ox	8.15	8.14
Ox	8.4	8.384
Horse	8.31	8.28
Pig	7.88	7.85
Pig	8.63	8.58

not always possible to observe this rule. We fixed the time at 11 a. m. and took the blood as near that time as possible. The blood was received in a capillary tube and put into a refrigerator until coagulation had taken place. Any serum which was found to be tinged with red was discarded. A temperature of 17.5 C. was maintained by means of the regulator connected with the apparatus. The examinations were made almost exclusively on recently admitted patients, since the use of aperients, such as sulphate of magnesia, is thought to increase somewhat the concentration of the blood.

The results of our examinations may be tabulated as shown in Table 2.

TABLE 2.—AUTHORS' ESTIMATIONS

No.	Name	Sex*	Age	Length of Time between Onset and Examination	Refractive Index	Protein, per Cent.
1	Y. Z.	♂	24	1 month	1.3540	10.4
2	N. M.	♂	1.3539	10.4
3	O. H.	♂	18	1.3526	9.5
4	Y. M.	♂	19	10 days	1.3525	9.5
5	H. M.	♂	19	5 to 6 days	1.3515	9.1
6	F. K.	♂	22	5 to 6 days	1.3515	9.1
7	S. M.	♂	23	3 weeks	1.3512	8.9
8	N. Y.	♂	56	4 months	1.3510	8.8
9	T. T.	♂	55	3 weeks	1.3505	8.5
10	Y. T.	♂	29	3 months	1.3498	8.1
11	S. R.	♂	20	20 days	1.3498	8.1
12	K. N.	♂	20	1.3488	7.5
13	O. T.	♂	37	1.3485	7.4
14	K. T.	♂	43	4 months	1.3477	6.8
15	M. T.	♂	27	1.3475	6.8
16	F. S.	♂	54	1 month	1.3472	6.6
17	M. T.	♂	51	1.3470	6.5
18	T. S.	♂	16	1 week	1.3468	6.3
19	T. S.	♂	49	1.3465	6.1
20	Y. S.	♀	24	2 weeks	1.3520	9.4
21	S. K.	♀	28	2 weeks	1.3517	9.2
22	S. T.	♀	41	1 month	1.3506	8.6
23	S. K.	♀	61	1½ months	1.3502	8.4
24	O. K.	♀	29	1 month	1.3500	8.2
25	S. K.	♀	20	5 to 6 days	1.3499	8.2
26	S. S.	♀	23	1.3495	7.9
27	Y. T.	♀	43	6 months	1.3495	7.9
28	H. I.	♀	34	2 months	1.3495	7.9
29	I. Y.	♀	22	1 month	1.3493	7.8
30	K. T.	♀	42	1 week	1.3489	7.6
31	K. I.	♀	33	40 days	1.3489	7.6
32	A. T.	♀	24	5 to 6 days	1.3486	7.4
33	I. N.	♀	47	1.3480	7.0
34	S. M.	♀	41	2 months	1.3479	7.0

* ♂ = male; ♀ = female.

As the table shows, the quantity of protein in the serum of thirty-four patients with beriberi, as computed from the refractive index, varied from 6.1 to 10.4 per cent. For purposes of comparison, we give, in Table 3, the results of several other authors.

TABLE 3.—REFRACTOMETRIC ESTIMATIONS OF OTHER AUTHORS FOR COMPARISON

Author	Refractive Index	Protein, per Cent.
Reiss.....	1.34802-1.35145	7.0-9.0
Strauss, Chajes.....	1.3480 -1.3510	7.0-8.7
Engel.....	1.3487 -1.3522	7.4-9.4
Martins.....	1.3480 -1.3520	7.0-9.0
Goldammer.....	1.34724-1.35169	6.6-9.1
Böhme.....	1.3476 -1.3512	6.8-8.9
Winternitz.....	1.34940-1.35058	7.8-8.5
Widal, Bernard, Vaucher.....	1.34904-1.35042	7.6-8.4
Tranter, Rowe.....	6.7-8.7

TABLE 4.—SERUM OF HEALTHY PERSONS

Number	Name	Sex*	Age	Refractive Index	Protein, per Cent.
1	O. C.	♂	20	1.3507	8.6
2	Y. K.	♂	36	1.3483	7.2
3	H. I.	♂	32	1.3483	7.2
4	I. K.	♂	56	1.3477	6.9
5	Y. M.	♂	10	1.3476	6.8
6	M. T.	♂	34	1.3473	6.6
7	T. N.	♂	21	1.3469	6.4
8	T. Z.	♂	30	1.3463	6.3
9	I. C.	♀	17	1.3490	7.6
10	M. S.	♀	68	1.3486	7.4
11	K. T.	♀	43	1.3479	7.0
12	T. F.	♀	16	1.3478	6.9
13	Y. T.	♀	30	1.3475	6.8
14	O. H.	♀	28	1.3469	6.4
15	K. F.	♀	17	1.3463	6.4

* ♂ = male; ♀ = female.

The figures for protein content in Table 3 vary from 6.6 to 9.4 per cent. If we assume that the normal protein content is found between 6.6 and 9.4 per cent., then the protein content of the beriberi blood

examined conformed in half the cases with the minimum normal figure but in the other half considerably exceeded the maximum normal figure. We examined as controls the serums of fifteen healthy Japanese. The results are given in Table 4.

The number of persons examined as controls was not large enough to warrant our accepting the figures obtained as representing the standard in healthy persons, yet it seems probable that the standard approaches these figures. A comparison of the figures in Table 4 with those of Table 2 apparently shows that the refractive index of the serum of persons suffering from beriberi is in general higher than that of normal persons. From Table 5, in which the average amount of protein for healthy and for beriberi serum is compared, it is clear that the quantity of protein in beriberi serum is greater than that of normal serum, irrespective of sex.

TABLE 5.—COMPARISON OF SERUMS FROM NORMAL PERSONS AND BERIBERI PATIENTS

	Average in Male, per Cent.	Average in Female, per Cent.	Total Average, per Cent.
Healthy serum.....	7.0	6.96	6.92
Beriberi serum.....	8.11	8.06	8.01

SUMMARY

The investigation reported in the foregoing account was made on the assumption that the rise in the refractive index of the serum in beriberi is dependent only on the increase of its protein content. It is possible, however, that it is also due to the retention of nonprotein substances. We may state in conclusion that the refractive index of the serum of persons suffering from beriberi shows often no deviation from the normal, but not infrequently a marked rise.

II. DETERMINATION OF UREA IN THE BLOOD AND OF AMBARD'S COEFFICIENT

Urea in the Blood.—Although the elimination of urea in beriberi has frequently been the subject of study, so far no results of studies on urea in the blood in these cases have been reported. The reason is probably that for ordinary methods a comparatively large quantity of blood is required. Moreover, the necessarily complicated technic makes such study impracticable. Both of these obstacles are removed,

however, in the method of determination of urea in the blood by means of urease reported by Van Slyke, Zacharias, and Cullen⁶ in 1914.

The results reported in the present paper were obtained by estimations of urea in the blood, according to the urease method, of both inpatients and outpatients of the Tokyo Municipal Charity Hospital. The urease was prepared by Bertrand's method, because in a preliminary comparison of samples of urease prepared (a) by the method of Hahn and Saphra,⁷ (b) by the method of Van Slyke, Zacharias, and Cullen,⁶ and (c) by Bertrand's method,⁸ the urease prepared by the latter method was found most active. The determination of the quantity of urea, however, was made after Hahn and Saphra, because their method was simplest. The blood was taken from inpatients

TABLE 6.—AMOUNT OF UREA IN BERIBERI BLOOD

Outpatients								Inpatients			
No.	Name	Sex†	Urea, per Mille	No.	Name	Sex†	Urea, per Mille	No.	Name	Sex†	Urea, per Mille
1	A.	♂	0.2	12	M.	♂	0.4	23	U.	♂	0.23
2	K.	♂	0.3	13	S.	♂	0.41	24	O.	♂	0.24
3	A.	♂	0.3	14	Y.	♂	0.42	25	O.	♀	0.25
4	M.	♂	0.32	15	K.	♂	0.45	26	S.	♂	0.28
5	K.	♂	0.32	16	M.	♂	0.46	27	O.	♀	0.29
6	T.	♀	0.32	17	H.	♂	0.49	28	S.	♀	0.30
7	O.	♂	0.32	18	K.	♂	0.50	29	O.	♂	0.33
8	S.	♂	0.34	19	K.	♂	0.50	30	H.*	♂	0.45
9	O.	♂	0.36	20	M.	♂	0.52	31	A.*	♂	1.03
10	F.	♂	0.37	21	O.	♂	0.6	32	H.*	♂	1.1
11	K.	♂	0.38	22	S.	♀	0.6	33	K.*	♂	5.79

* These patients were severe cases. A. and K. died from cardiac failure, not infrequent in beriberi. The remaining two were discharged after gradual recovery.

† ♂ = male; ♀ = female.

before breakfast and from outpatients at 11 a. m. The results are given in Table 6.

The quantity of urea in the twenty-two outpatients varied from 0.2 to 0.6 gm. per liter, an average of 0.3 to 0.4 being general. In the seven mild house cases, the quantity varied from 0.23 to 0.33 gm. per

6. Van Slyke, D. D., Zacharias, G., and Cullen, G. E.: Die Darstellung fester Urease und ihre Verwendung zur quantitativen Bestimmung von Harnstoff im Harn, Blut, und in der Zerebrospinalflüssigkeit, Deutsch. med. Wchnschr., 1914, 40, 1219.

7. Hahn, A., and Saphra, J.: Ein einfache für die Praxis geeignete Methode zur quantitativen Bestimmung des Harnstoffs im Urin, Deutsch. med. Wchnschr., 1914, 40, 430.

8. Bertrand: Practical Physiological Chemistry (Japanese translation).

liter. Three out of four severe house cases showed a considerable retention of urea—5.79 gm. per liter in one case.

Table 7 gives the figures obtained by several workers for determinations of urea in healthy blood.

Apparently, then, the normal amount of urea in the blood varies from 0.2 to 0.6 gm. per liter. One of us (Nemoto) obtained practically the same figures (0.2 to 0.56 gm. per liter) from twenty-one patients without renal disease and two healthy persons. As shown in Table 6, the urea content of the blood in mild cases of beriberi was within normal limits, but in severe cases it not only increased to more than 1.0 gm. per liter, but in one case rose beyond 5.0 gm. per liter. This case recalls one reported by M. Miura⁹ several years ago, in which he estimated 5.0 gm. per liter of urea in the pleural and peritoneal effusion from a case of beriberi. Miura, however, did not estimate the urea in the blood. Such a deviation from the normal appearing in severe cases may be due to a combination of two causes: (1) lessened elimination of urine as a result of weakened heart action, and (2) increased pro-

TABLE 7.—QUANTITY OF UREA IN HEALTHY BLOOD

Author	Urea, Gm. per Liter	
Schöndorff.....	0.23-0.505	
Schöndorff.....	1.5	(After the intake of a large quantity of protein)
Jaksch.....	0.3-0.6	
McLean.....	0.2-0.5	(Estimated with urease)

tein metabolism (K. Miura, Y. Teruchi, and others), but which of these two is the main cause cannot be stated without further study.

Ambard's Coefficient.—Ambard's law with regard to kidney function has been confirmed by several workers. The details of the subject are well known and will not be recounted here. Ambard has reported that the coefficient in healthy persons ranges from 0.06 to 0.07, and that the coefficient is higher as the deviation in kidney function is greater. McLean,¹⁰ who used urease for the determination of urea in his study of the subject, suggests 0.08 as the coefficient in healthy persons.

The results obtained by us with cases of beriberi are as shown in Table 8.

9. Miura, K.: Beriberi, 1913.

10. McLean, F. C.: The Numerical Laws Governing the Rate of Excretion of Urea and Chlorid in Man. I. An Index of Urea Excretion and the Normal Excretion of Urea and Chlorid. II. The Influence of Pathological Condition and of Drugs on Excretion, Jour. Exper. Med., 1915, **22**, 212, 366.

Ambard's coefficient ranged from 0.07 to 1.36, and in the majority of cases was above 0.09. If we take 0.08 as the normal coefficient — and our controls confirm McLean's results — then the coefficient in beriberi cases is greater than the normal. The rise of the coefficient does not necessarily coincide with the severity of clinical manifestations, for some mild cases showed a coefficient of 0.13 or 0.14, and some severe cases 0.07 or 0.08. It appears that in comparatively mild cases the function excreting urea may be disturbed, while in severe cases it may not be affected. It is worthy of note that in two out of four severe cases which showed a normal coefficient the patients afterward recovered, while the two patients who had a high coefficient died.

TABLE 8.—AMBARD'S COEFFICIENT IN BERIBERI CASES

No.	Name	Nature of Case	Wt., Kg.	Urine, 24 Hrs.		Urea in Blood, Gm. Liter	Urea in Urine, per Cent.	Coefficient	Remarks
				C.c.	Gm.				
1	K.	Severe	60	1,350	18.79	5.79	13.91	1.36	Died
2	A.	Severe	60	1,410	40.25	1.03	28.46	0.14	Died
3	H.	Severe	40	3,020	105.92	1.10	35.09	0.08	Recovered
4	H.	Severe	52	1,605	32.28	0.45	20.11	0.07	Recovered
5	S.	Mild	36	1,550	6.51	0.30	4.20	0.14	Recovered
6	O.	Mild	51	384	8.91	0.29	23.21	0.08	Recovered
7	O.	Mild	42	840	6.92	0.33	8.23	0.13	Recovered
8	U.	Mild	41	624	4.77	0.23	7.64	0.10	Recovered
9	O.	Mild	36	864	8.05	0.25	9.31	0.09	Recovered
10	O.	Mild	49	1,728	13.27	0.24	7.68	0.08	Recovered
11	S.	Mild	54	1,152	12.40	0.28	10.76	0.09	Recovered
C*	M.	Normal	53	792	10.95	0.25	13.82	0.08	
C*	K.	Normal	48	1,066	14.11	0.27	12.01	0.08	

* Control.

These instances seem to suggest that the cardiac failure in beriberi may be due to uremia, yet the clinical symptoms in cases of cardiac failure in beriberi are quite different from those of the ordinary uremia. It is possible that in beriberi some unknown toxic substances are produced in the blood which, if excreted in the same manner as urea, do not cause death, but the accumulation of which in the blood causes heart failure. If this is true, then it is conceivable that the amelioration of the threatening symptoms of beriberi which venesection brings is the result of diminution of the unknown toxic products. Further investigation of this subject is necessary before a definite statement can be made.

SUMMARY

1. The quantity of urea in the blood of beriberi patients shows, in mild cases, no deviation from the normal, but in the majority of severe cases a marked increase.
2. Ambard's coefficient is not infrequently higher than normal in beriberi; that is, the function excreting urea is frequently disturbed.
3. The disturbance of the kidney function does not necessarily coincide with the gravity of the clinical manifestations.
4. Even in cases in which the clinical symptoms are severe, if the function excreting urea is intact, the prognosis is hopeful.
5. It is possible that cardiac failure in beriberi is due to an accumulation of some unknown toxic products in the blood, the elimination of which is coincident with the elimination of urea.

A STUDY OF RENAL FUNCTION IN PATIENTS CONVALESCING FROM ACUTE FEVERS *

ARTHUR BOOKMAN, M.D.

NEW YORK

The newer methods of functional kidney examination make it possible to secure evidence of renal disturbance formerly not obtainable. In grave and advanced forms of acute and chronic nephritis this information has proved its value. In the borderline cases, the milder disturbances of the kidney often unrevealed by older methods, we would expect functional tests to be of still greater aid in diagnosis and prognosis.

The slight albuminuria of the acute infectious fevers, often accompanied by hyaline casts and commonly disappearing with the fever, may be taken as a type of the disturbances referred to. A sharp line has usually been drawn between this "febrile albuminuria" and true nephritis. It is the common impression that this accompanying albuminuria, if it disappears with or shortly after the fever, is accompanied by no important renal change and is never of serious import.

It appears of value at this time to consider the effect of the acute fevers and of febrile albuminuria on renal function, and if we find that this is disturbed, to inquire how long the impairment lasts. We should gain in this way a truer estimate than was heretofore possible of the importance of the renal syndrome in the subsequent history of the individual.

For these reasons the functional tests here reported were made on patients during or after convalescence from acute fevers. In all but two of the patients studied, and these are included mainly for comparison, the effect of the fever on the kidneys, judged from the clinical symptoms and the ordinary clinical urine examination during the fever, was either none at all or the production merely of a mild febrile albuminuria. One patient, however, had edema of the face and extremities, with slight urinary changes, several weeks after a tonsillitis. Another had a prolonged fever due to a staphylococcus meningitis. During the fever there was a distinct nephritis, but the urine had been normal for

* Submitted for publication Feb. 17, 1917.

* From the Second Medical Service and the Department of Physiologic Chemistry, Pathologic Laboratory, Mount Sinai Hospital, and the Chemical Laboratory, Montefiore Home and Hospital.

* Read before the Section on Medicine, New York Academy of Medicine, April 17, 1917.

a month before the tests were made. In most of the other patients the urine had been normal a number of days before the tests.

The tests were made, as a rule, shortly before the patient left the hospital, and from three to fifteen days after the temperature had become normal. In only two cases was it possible to follow the patient after discharge. The results of the estimation of phenolsulphone-phthalein excretion and of the examination of two-hour specimens of urine after a test diet as outlined by Dr. Mosenthal¹ are of especial interest. In estimating the degree of impairment, the standards recently given by Mosenthal and Lewis² have been used. In Table 16 the results are summarized, slight impairment being denoted by figures in parentheses, moderate impairment by heavy faced type.

Over one-half of the patients had some degree of nocturnal polyuria. This was seldom of a high grade. There are no reports from other sources in regard to this criterion of renal function in cases similar to those herein reported. In indicating impaired kidney function, it is, however, of undoubted value.

The changes shown in the two-hour phthalein excretion are most striking, and but few other observations could be found in similar conditions.

Rowntree and Geraghty,³ during typhoid fever, found an excretion of 45.5 per cent. In a fatal case of pneumonia with gangrene they reported an excretion of 57 per cent., and a similar case examined by Thayer and Snowden⁴ there was an elimination of 27 per cent., and again 20 per cent. of the dye in two hours. At necropsy the changes in the kidneys were similar in both, one showing a "fatty degeneration" and the other "cloudy swelling." Incidental to their study of renal function in serum disease, Longcope and Peters⁵ studied the phthalein excretion in a few cases of pneumonia. Before crisis they found in one case 26 per cent. and later 50 per cent.; in another 56 per cent., and after crisis in the same patient 51 per cent. Another patient after crisis eliminated 64 per cent.

Observations published by Lewis⁶ while this paper was in preparation are of especial interest. He finds a marked increase (average excretion 70.5 per cent.) common to all fevers. This is associated with increased functional activity of the kidneys as evidenced by an enormous increase in the rate of output of urea. Determinations made after the temperature had been normal for four days showed a marked

-
1. Mosenthal, H. O.: *THE ARCHIVES INT. MED.*, 1915, **16**, 733.
 2. Mosenthal and Lewis: *Jour. Am. Med. Assn.*, 1916, **67**, 933.
 3. Rowntree and Geraghty: *THE ARCHIVES INT. MED.*, 1912, **9**, 284.
 4. Thayer and Snowden: *Am. Jour. Med. Sc.*, 1914, **148**, 781.
 5. Longcope and Peters: *THE ARCHIVES INT. MED.*, 1916, **18**, 496.
 6. Lewis: *THE ARCHIVES INT. MED.*, 1917, **19**, 1.

return to normal of both urea and phthalein output, the latter averaging 63 per cent. Determinations of phthalein output during convalescence were made by him on three patients with typhoid fever and were as follows:

Case	Days after Fever	Two-Hour Dye Excretion Per Cent.
409	During fever	68
	20	59
	60	65
	6 months	69
411	During fever	78
	7	81
416	6	50

In general, then, previous observations show a certain amount of disturbance of phthalein excretion during fever, while observations during convalescence are too scanty to justify any generalizations.

Of our fifteen patients, only three had a phenolsulphonephthalein excretion of over 60 per cent. One of these, Case 15, is the same patient convalescent from a meningitis to whom reference has previously been made and who undoubtedly had a chronic nephritis. In five instances the concentration was well below 40 per cent., the lowest being 27 per cent. In one patient there was hyperpermeability for the dye, the excretion being 88 per cent. (Case 3).

On the test diet, fixation of the specific gravity of the two-hour specimens was noted only once — in a young man (Case 10) recovering from pneumonia, who, in childhood, had had scarlet fever. In three patients (Cases 3, 10 and 15) there was an indication of fixation of the quantity of the two-hour specimens. One of these was the meningitis patient (Case 15), whose urine during the fever period indicated a true nephritis.

Most of the patients had a normal concentration of salt in the two-hour specimens. In three cases (5, 7 and 11) it was somewhat lowered. Our observations, however, bring out some suggestions of interest in the chlorid metabolism, though they cannot, of course, be regarded as giving accurate balances.

It has been shown repeatedly by others that there is retention of chlorids during the course of acute fevers, and that this is followed by an increased elimination during convalescence. These changes are extreme in pneumonia. But in malaria, during the paroxysm, chlorid excretion is greatly increased. In most of the patients a chlorid deficit, or at least an approximate balance, was therefore to have been expected. On the Mosenthal test diet in normal controls the sodium chlorid in the urine for the twenty-four-hour period about equals or exceeds the intake. Many of the patients, we must assume, had for elimination sodium chlorid stored up during the fever, in addition to that contained in the food. Yet we find that most of them excreted

considerably less even than their intake of approximately 9.0 gm. This does not agree with the increased elimination of chlorids after fever, which many other observers have found. Most of our patients certainly retained salt during the test. This may be due in part to diminished kidney efficiency, or it may be associated with the gain in weight which takes place during convalescence. To decide on the importance of the former factor it would have been valuable to observe the manner of excretion of salt added to the diet.

A low, fixed salt concentration, it is well known, is one of the early signs of kidney impairment. It is my impression that lowered kidney function is at least partly responsible for the very marked retention and the low concentration of salt in the urine during the fever of pneumonia, because not only is the salt concentration low at this stage, but also, as von Moraczewski⁷ has shown, there is scarcely any increase in the excretion, if 5 or 10 gm. are added to the food. If this low concentration during the fever is due, as seems likely, to the inability of the kidney to excrete salt in higher concentration, one would expect to find some indication of this lowered power during convalescence as well, such as our patients show.

In the blood, incoagulable nitrogen and urea nitrogen were determined. No striking changes were found. The great destruction of nitrogenous bodies which takes place during fever makes the interpretation of slight changes difficult. These findings are therefore given without discussion. Uric acid was estimated in two patients, and in both the amount in the blood was moderately elevated. Both patients showed other signs of renal disturbance. More information as to this factor would be of interest in view of the conclusion of Myers and Fine,⁸ that in chronic nephritis, uric acid is the first of the nitrogenous bodies to show an increase in the blood. Its increase in gout they also ascribe to renal disturbance. The finding of increased amounts after fever suggests that it would be of interest to investigate to what extent the accumulation in gout depends on the fever of the acute attacks.

METHODS

Phenolsulphonephthalein Test: Technic of Rowntree and Geraghty.⁹

Blood: 1. Urea: Van Slyke and Cullen's modification of Marshall's method.¹⁰ 2. Incoagulable Nitrogen: Greenwald.¹¹ 3. Uric Acid: Dr. T. Kuttner's microcolorimetric modification of the Folin method (about to be published).

7. Von Moraczewski: *Ztschr. f. klin. Med.*, 1900, **39**, 44.

8. Myers and Fine: *Jour. Biol. Chem.*, 1915, **20**, 931; also Chase and Myers: *Jour. Am. Med. Assn.*, 1916, **67**, 929.

9. Rowntree and Geraghty: *THE ARCHIVES INT. MED.*, 1912, **10**, 284.

10. Van Slyke and Cullen: *Jour. Biol. Chem.*, 1914, **19**, 211.

11. Greenwald: *Jour. Biol. Chem.*, 1915, **21**, 61.

Test Diet: The technic followed closely that described by Dr. Mosenthal. The diet employed was analyzed repeatedly. The nitrogen content was about 13.7 gm. The salt content varied somewhat and averaged about 9.0 gm. The diet was, as a rule, given for two days instead of one, and the specimens were collected on the second day.

The following table, extracted from one given by Mosenthal and Lewis,² is useful for interpretation of results.

SCALE OF IMPAIRMENT OF RENAL FUNCTION AS INDICATED BY TESTS EMPLOYED

Degree of Impairment of Renal Function	Phenolsulphone-phthalein Per Cent.	Test Meal for Renal Function			
		Night c.c.	Urine Sp. Gr.	Variation in the Highest is	Sp. Gr. When 1.017-1.015
Normal	—	400	1.018+	9+	
Slight	+	401-600	1.016 and 1.017	8-5	6+
Moderate	++	601+	1.015	4	5 and 4
Marked	+++				3
Maximal	++++				

DISCUSSION

Prognostic Considerations.—In considering the results of tests of renal function one cannot emphasize too much that they yield no absolute conclusions as to the kind and degree of histologic damage the kidneys have sustained. This was brought out by Schlayer¹² early in the modern study of renal physiology. Severe functional impairment may be transitory, or it may be dependent on factors outside the kidney. Severe histologic damage may or may not be attended by functional disturbance of the same degree, but it is likely to persist. If the functional tests could have been repeated in my patients at intervals after convalescence, many of the changes would have been seen to disappear quickly. If this were not the case, one would have to assume that in most individuals a nocturnal polyuria and a lowered phthalein index are permanent after acute fevers. Persistence of such changes would certainly indicate a chronically damaged kidney. There is a suggestion of such damage in Case 8, months after the original disease; while in Case 15 the kidneys evidently failed to recover their normal functional capacity.

On the other hand, it is clear that functional tests will often reveal a nephritis which would not be recognized by other methods of examination. Absence of albumin and casts after fever is not a guarantee that the kidneys are normal. Case 15 again shows this in a striking manner. Febrile albuminuria, I believe, is usually dependent on an actual nephritis, and my results justify the conclusion that the albumin disappears long before the kidneys have recovered completely. It is clear from this that recovery can best be gaged by repeating functional tests at intervals during and after convalescence. It is probable that in this way a chronic nephritis will not rarely be found to date back to some apparently trifling febrile albuminuria.

12. Schlayer: z. Med. Klin., Beiheft., 1912, 8, 211.

Diagnosis.—In this series the phthalein test showed a much more apparent disturbance than the other methods employed. This is contrary to the results usually obtained in chronic nephritis,¹³ in which the dietetic test usually shows disturbance much earlier than the other methods. Dye excretion as low as 27 per cent. was found with kidneys which clinically must be pronounced sufficient. In a nephritic patient such values are usually accompanied by nitrogen accumulation in the blood, and are of serious import.¹⁴ In the absence of cumulative phenomena and of other confirmatory clinical evidence, extreme caution is therefore to be exercised in concluding from lowered phthalein excretion that the kidneys are seriously diseased. This is true, especially in patients who have recently had an acute febrile disease, even though other functional tests give some confirmatory evidence.

In chronic nephritis the same care is needed in the interpretation of results. Here one would expect fever to disturb function even more than in normal individuals. Under these circumstances a high degree of impairment of kidney efficiency might well be temporary, and a bad prognosis based mainly on functional tests would often prove fallacious.

SUMMARY AND CONCLUSIONS

Renal functional tests carried out on a series of patients after acute fevers lead to the following conclusions:

1. Without other signs of nephritis, most of them showed distinctly impaired function.
2. The greatest disturbance was shown by the phenolsulphone-phthalein test.
3. Nocturnal polyuria was also frequent, though usually slight.
4. In interpreting the results of functional renal tests, the influence of a preceding febrile disease must always be considered.

The prognostic and diagnostic importance of these facts is discussed.

The influence of fever on the concentration of uric acid in the blood and on the ability of the kidneys to concentrate sodium chlorid is discussed.

REPORTS OF CASES

CASE 1.—(163621.) Abraham F., aged 30. Previous history of no importance. Takes two drinks of whiskey a day.

Present illness, acute lobar pneumonia; temperature normal after May 20; blood pressure, systolic 110, diastolic 55.

Urine: Twenty-four-hour specimens, specific gravity, 1.010 to 1.030; albumin, a trace occasionally found, and in three of twelve specimens a few granular casts; quantity 650 to 1,500 c.c.

13. Mosenthal: Jour. Am. Med. Assn., 1916, **67**, 933; Christian, H. A.: discussion, *ibid.*

14. Elliott, A. R.: Jour. Am. Med. Assn., 1915, **64**, 1885.

TABLE 1.—DATA OF RENAL FUNCTION IN CASE 1

May 26, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	135	1.026	1.02	1.38	1.62	2.19
10 to 12 a. m.	55	1.029	0.85	0.47	1.74	0.96
12 to 2 p. m.	65	1.031	1.0	0.65	2.4	1.56
2 to 4 p. m.	100	1.030	1.11	1.11	1.4	1.4
4 to 6 p. m.	70	1.027	1.0	0.7	1.43	1.0
6 to 8 p. m.	100	1.026	0.82	0.82	1.68	1.68
Total day	525	0.97	5.13	8.79
8 p. m. to 8 a. m.	415	1.019	0.62	2.57	1.04	4.32
Total 24 hours	940	0.82	7.7	13.11

Blood: May 23, incoagulable nitrogen, 56 mg. per 100 c.c.; urea nitrogen, 30 mg. per 100 c.c.

Phthalein elimination May 23, per cent., first hour, 25; second hour, 19; two-hour total, 44.

Summary: Water retention; slight nocturnal polyuria; definitely impaired dye excretion.

CASE 2.—(163220.) Abraham W., aged 14. No previous illness. Acute lobar pneumonia lasting ten days. Crisis May 3. Blood Pressure, May 1, systolic 100, diastolic 60.

Urine: Twenty-four-hour specimens, quantity, 700 to 1,400 c.c.; acid; specific gravity, 1.020 to 1.028; albumin, +; hyaline casts repeatedly until crisis, then normal.

TABLE 2.—DATA OF RENAL FUNCTION IN CASE 2

May 10, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	225	1.007	0.25	0.56	0.46	1.04
10 to 12 a. m.	150	1.022	0.29	0.44	1.07	1.6
12 to 2 p. m.	65	1.026	0.51	0.33	1.54	1.0
2 to 4 p. m.	70	1.026	0.7	0.49	1.26	0.88
4 to 6 p. m.	85	1.023	0.48	0.41	1.85	1.57
6 to 8 p. m.	70	1.026	0.33	0.23	1.36	0.95
Total day	665	0.37	2.46	7.04
8 p. m. to 8 a. m.	375	1.024	0.78	2.93	1.54	5.78
Total 24 hours	1,040	0.51	5.39	12.82

At dinner, failed to take soup, green vegetable and half the bread and butter.

Phthalein elimination May 11, per cent., first hour, 16; second hour, 22; two-hour total, 38.

Summary: Retention of salt and water; moderately impaired dye excretion.

CASE 3.—(161488.) Israel E., aged 18. Previous history, no infectious diseases; frequent headaches.

Present illness, acute lobar pneumonia; crisis February 22. February 20, blood pressure, systolic 108, diastolic 55.

Urine: Single specimens, specific gravity, 1.019 to 1.024; albumin, faint trace during fever; none later; microscopically negative.

Blood: March 1, incoagulable nitrogen, 47 mg. per 100 c.c.; urea nitrogen, 14 mg. per 100 c.c.

TABLE 3.—DATA OF RENAL FUNCTION IN CASE 3

March 2, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	210	1.008	0.25	0.52	0.5	1.05
10 to 12 a. m.	220	1.009	0.26	0.57	0.45	1.0
12 to 2 p. m.	180	1.016	0.51	0.92	0.67	1.2
2 to 4 p. m.	210	1.013	0.44	0.93	0.57	1.19
4 to 6 p. m.	190	1.014	0.44	0.84	0.72	1.37
6 to 8 p. m.	110	1.017	0.39	0.43	0.94	1.03
Total day	1,120	0.37	4.21	6.84
8 p. m. to 8 a. m.	510	1.017	0.74	3.77	1.02	5.2
Total 24 hours	1,630	0.48	7.98	12.04

Phthalein elimination, per cent., first hour, 50; second hour, 38; two-hour total, 88.

Summary: The total water output and the night urine are increased. Salt concentration is low. The variation in specific gravity is nine points—just within normal limits. The value of these results is lessened because the dye test with its increased fluid intake seems to have been done on the same day as the urinary test meal. Dye excretion is increased.

CASE 4.—(162451.) Harry T., aged 14. Previous history, scarlet fever in early childhood. One brother has kidney trouble.

Present illness, acute lobar pneumonia lasting seven days; fever until April 2. Blood pressure, April 3, systolic 115, diastolic 60.

Urine: Repeated examination of twenty-four hour specimens, quantity, 700 to 1,000 c.c.; specific gravity, 1.028 to 1.030; albumin, faint trace; microscopically, once a few granular casts found; no casts in the remaining specimens.

TABLE 4.—DATA OF RENAL FUNCTION IN CASE 4

April 11, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	225	1.016	0.7	1.57	0.98	2.2
10 to 12 a. m.	80	1.021	0.73	0.58	1.07	0.86
12 to 2 p. m.	165	1.014	0.73	1.2	0.66	1.09
2 to 4 p. m.	135	1.020	1.08	1.46	0.82	1.1
4 to 6 p. m.	225	1.012	0.55	1.24	0.61	1.37
6 to 8 p. m.	70	1.023	0.62	0.43	1.35	0.95
Total day	900	0.72	6.48	7.57
8 p. m. to 8 a. m.	200	1.028	0.78	1.56	1.68	3.36
Total 24 hours	1,100	0.73	8.04	10.93

Phthalein elimination, per cent., first hour, 9.5; second hour, 30; two-hour total, 39.5.

Summary: Normal response to test diet; dye excretion moderately impaired.

CASE 5.—(162588.) Morris G., aged 32. Previous history, scarlet fever at 2 years; takes about two drinks of whiskey daily.

Present illness, acute lobar pneumonia lasting fourteen days.

Urine: Examination of single specimens, specific gravity, 1.018 to 1.024; albumin present; a few granular casts found occasionally during fever and once during convalescence.

Blood: April 23, incoagulable nitrogen, 53.9 mg. per 100 c.c.; urea nitrogen, 10.5 mg. per 100 c.c.; uric acid, 4.5 mg. per 100 c.c.

TABLE 5.—DATA OF RENAL FUNCTION IN CASE 5

April 22, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	240	1.009	0.39	0.94	0.61	1.46
10 to 12 a. m.	40	1.015	0.64	0.25	0.63	0.25
12 to 2 p. m.	220	1.010	0.37	0.81	0.46	1.0
2 to 4 p. m.	30	1.013	0.62	0.19	0.56	0.17
4 to 6 p. m.	200	1.012	0.48	0.96	0.54	1.08
6 to 8 p. m.	55	1.015	0.41	0.22	0.64	0.36
Total day	785	0.43	3.37	4.33
8 p. m. to 8 a. m.	640	1.013	0.33	2.11	0.69	4.42
Total 24 hours	1,425	5.48	8.75

Phthalein elimination, April 23, per cent., first hour, 40; second hour, 15; two-hour total, 55.

Summary: The microscopic examination of the urine shows a slight nephritis. After the test diet the specific gravity is low and the variations are below normal. There is a tendency to fixation in concentration of salt and of nitrogen. The night urine shows moderate increase in amount, low salt and nitrogen concentration; dye excretion slightly impaired.

CASE 6.—(161930.) George S., aged 32. Previous history; typhoid fever in childhood.

Present illness, acute lobar pneumonia lasting nine days, with icterus. Crisis March 18. From April 1 to 9, slight fever again with a macular rash; diagnosis doubtful. Blood pressure, April 11, systolic 80, diastolic 45.

Urine: Twenty-four-hour specimens, specific gravity, 1.014 to 1.022; quantity, 700 to 1,100 c.c.; albumin present during fever and at times hyaline casts; both absent during afebrile periods; bile present during pneumonia.

Blood: March 12, incoagulable nitrogen, 62.8 mg. per 100 c.c.; urea nitrogen, 17.5 mg. per 100 c.c.; April 22, incoagulable nitrogen, 36.4 mg. per 100 c.c.; urea nitrogen, 8.4 mg. per 100 c.c.; uric acid, 5.2 mg. per 100 c.c.

TABLE 6.—DATA OF RENAL FUNCTION IN CASE 6

April 21, 1916	Quantity, C.c.	Specific Gravity.	Sodium Chlorid—		Nitrogen—	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	75	1.018	0.74	0.55	0.71	0.53
10 to 12 a. m.	90	1.017	0.88	0.8	0.75	0.68
12 to 2 p. m.	190	1.006	0.18	0.34	0.29	0.55
2 to 4 p. m.	50	1.017	0.62	0.31	0.71	0.35
4 to 6 p. m.	190	1.011	0.32	0.61	0.52	0.99
6 to 8 p. m.	110	1.012	0.39	0.43	0.4	0.44
Total day	705	0.43	3.04	3.54
8 p. m. to 8 a. m.	435	1.016	0.56	2.44	0.52	2.26
Total 24 hours	1,140	0.48	5.48	5.8

Phthalein elimination, per cent., first hour, 30; second hour, 10; two-hour total, 40.

Summary: Slight nocturnal polyuria; slightly impaired dye excretion; water and salt retention.

CASE 7.—(163362.) Isidore K., aged 12½. Previous history, tonsillitis one year before.

Present illness began April 15 with chills, pains in chest and fever; temperature became normal May 6, three days after admission; physical signs of pleurisy with effusion. Blood pressure, systolic 105, diastolic 50.

Urine: Twenty-four-hour specimens, specific gravity, 1.015 to 1.025; albumin, a faint trace found twice only; no casts.

Blood: May 12, incoagulable nitrogen, 37 mg. per 100 c.c.; urea nitrogen, 23 mg. per 100 c.c.

TABLE 7.—DATA OF RENAL FUNCTION IN CASE 7

May 10, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid—		Nitrogen—	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	220	1.017	0.46	1.01	0.82	1.8
10 to 12 a. m.	85	1.023	0.48	0.41	1.33	1.12
12 to 2 p. m.	60	1.018	0.53	0.32	0.96	0.58
2 to 4 p. m.	100	1.018	0.42	0.42	1.02	1.02
4 to 6 p. m.	180	1.011	0.2	0.36	0.69	1.24
6 to 8 p. m.	170	1.017	0.23	0.39	1.4	2.38
Total day	815	0.35	2.91	8.14
8 p. m. to 8 a. m.	250	1.021	0.59	1.49	1.3	3.33
Total 24 hours	1,065	0.41	4.4	11.47

At 12, failed to take soup, green vegetable and half the bread.

Phthalein elimination, per cent., first hour, 18; second hour, 16; two-hour total, 34.

Summary: There is a tendency toward fixation in the salt excretion. The total salt output is low. Dye excretion is moderately impaired.

CASE 8.—(163002.) Hyman A., aged 24. Past history negative.

Present illness, typhoid with fever lasting until May 5.

Blood pressure, systolic 125, diastolic 60.

Urine: Twenty-four-hour specimens, quantity 850 to 2,000 c.c.; specific gravity, 1.010 to 1.022; albumin present from May 1 to 9 only; no casts at any time.

Blood: May 11, incoagulable nitrogen, 45.7 mg. per 100 c.c.; urea nitrogen, 35 mg. per 100 c.c.

Phthalein elimination, May 11, per cent., first hour, 12; second hour, 15; two-hour total, 27.

TABLE 8a.—DATA OF RENAL FUNCTION IN CASE 8

May 14, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid— Per Cent. Gm.		Nitrogen— Per Cent. Gm.	
8 to 10 a. m.	100	1.018	0.51	0.51	1.01	1.01
10 to 12 a. m.	85	1.018	0.61	0.52	1.02	0.87
12 to 2 p. m.	70	1.023	0.62	0.43	1.29	0.9
2 to 4 p. m.	100	1.024	0.75	0.75	1.13	1.13
4 to 6 p. m.	150	1.016	0.35	0.55	0.95	1.42
6 to 8 p. m.	230	1.010	0.19	0.44	0.53	1.2
Total day	735	0.43	3.2	6.53
8 p. m. to 8 a. m.	420	1.017	0.51	2.14	1.2	5.04
Total 24 hours	1,155	0.46	5.34	11.57

Summary: Slight nocturnal polyuria; slight water and salt retention; dye excretion moderately impaired.

This patient (Case 8) was seen again Dec. 25, 1916. He had been well in the interval. The urine was collected at two-hour intervals. Food and fluids were not limited. Meals were taken at 8, 12 and 5, and no fluid was taken except at meals.

Urine: Albumin, none; microscopically negative. Table 8b shows the other data:

TABLE 8b.—DATA OF RENAL FUNCTION IN CASE 8

Dec. 25, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid— Per Cent. Gm.		Nitrogen— Per Cent. Gm.	
8 to 10 a. m.	70	1.035	0.67	0.47
10 to 12 a. m.	135	1.029	1.38	1.86
12 to 2 p. m.	140	1.028	1.48	2.06
2 to 4 p. m.	175	1.026	1.62	2.83
4 to 6 p. m.	125	1.030	1.44	1.8
6 to 8 p. m.	120	1.030	1.22	1.46
Total day	765	10.48	1.66	12.7
8 p. m. to 8 a. m.	440	1.030	1.31	5.76	1.86	8.2
Total 24 hours	1,205	16.24	20.9

Phthalein elimination, December 26, per cent., first hour, 40; second hour, 10; two-hour total, 50.

Summary: More than seven months after his acute illness the patient still shows a slight nocturnal polyuria and slightly impaired dye excretion.

It is unfortunate that the diet in this determination could not be better controlled. In spite of this, the results indicate that kidney function is not yet entirely normal.

CASE 9.—(162806.) Abraham B., aged 25. Previous history, had pneumonia as a young boy.

Present illness, typhoid fever; temperature normal after May 4. Blood pressure, April 19, systolic 110, diastolic 70. Blood examination, April 14, hemoglobin, 110 per cent.; erythrocytes, 5,760,000.

Urine: Twenty-four-hour specimens, quantity, 600 to 1,600 c.c.; specific gravity, 1.012 to 1.022; albumin at times in a very faint trace; microscopically negative.

Blood: May 11, incoagulable nitrogen, 40 mg. per 100 c.c.; urea nitrogen, 11.2 mg. per 100 c.c.

TABLE 9.—DATA OF RENAL FUNCTION IN CASE 9

May 14, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid— Per Cent. Gm.		Nitrogen— Per Cent. Gm.	
8 to 10 a. m.	220	1.016	0.94	2.07	0.72	1.58
10 to 12 a. m.	135	1.017	0.73	0.99	0.65	0.88
12 to 2 p. m.	110	1.019	1.03	1.13	0.8	0.88
2 to 4 p. m.	150	1.017	0.78	1.17	0.8	1.2
4 to 6 p. m.	230	1.011	0.43	0.99	0.41	0.94
6 to 8 p. m.	185	1.011	0.34	0.63	0.51	0.94
Total day	1,030	0.68	6.98	6.42
8 p. m. to 8 a. m.	440	1.017	0.46	2.02	0.44	1.93
Total 24 hours	1,470	9.00	8.35

Phthalein elimination, May 11, per cent., first hour, 10; second hour, 17; two-hour total, 27.

Summary: Slight nocturnal polyuria; moderately impaired dye excretion.

CASE 10.—(161140.) Joseph G., aged 26. No previous illness. In the hospital from Jan. 18 to 24, 1916, with temperature up to 101.4 F., and a papular rash on the trunk. The Widal reaction was negative.

Urine: Specific gravity, 1.018 to 1.025; an occasional granular cast found in the first specimen after admission only.

Readmitted February 2 with a typical typhoid fever. Temperature normal after February 16.

Urine: Single specimens examined daily. Specific gravity 1.012 to 1.026; albumin, usually none; at times a faint trace; on only one examination were hyaline casts found.

Blood pressure, February 4, systolic 95, diastolic 55.

February 3, hemoglobin 65 per cent.; erythrocytes 3,264,000.

March 4, incoagulable nitrogen 59 mg. per 100 c.c. blood; urea nitrogen 18 mg. per 100 c.c. blood.

TABLE 10.—DATA OF RENAL FUNCTION IN CASE 10

March 3, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid—		Nitrogen—	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	230	1.012	0.82	1.89	0.59	1.36
10 to 12 a. m.	235	1.012	0.82	1.93	0.45	1.05
12 to 2 p. m.	200	1.005	0.35	0.7	0.23	0.46
2 to 4 p. m.	225	1.007	0.43	0.97	0.24	0.54
4 to 6 p. m.	220	1.010	0.57	1.25	0.45	0.99
6 to 8 p. m.	100	1.021	0.97	0.97	0.87	0.87
Total day	1,210	0.63	7.71	5.27
8 p. m. to 8 a. m.	580	1.016	0.82	4.76	0.66	3.83
Total 24 hours	1,790	0.69	12.47	9.1

Phthalein elimination, March 4, per cent., first hour 33; second hour 23; two-hour total 56.

Summary: Definite polyuria throughout the test; unusually large salt output. There is a tendency to fixation in the amount of the two-hour urine. Almost normal dye excretion.

CASE 11.—(163259.) Rose L., aged 33. Previous history negative.

Present illness, typhus fever. The temperature reached normal May 6. Blood pressure, systolic 100, diastolic 70.

Urine: Twenty-four-hour quantity about 1,000 c.c.; specific gravity 1.010 to 1.020; albumin at times in faint trace; no casts.

TABLE 11.—DATA OF RENAL FUNCTION IN CASE 11

May 9, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid—		Nitrogen—	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	90	1.015	0.43	0.39	0.85	0.77
10 to 12 a. m.	70	1.016	0.47	0.33	0.46	0.32
12 to 2 p. m.	350	1.017	0.12	0.42	0.3	1.05
2 to 4 p. m.	150	1.015	0.25	0.38	0.59	0.89
4 to 6 p. m.	130	1.015	0.26	0.34	0.72	0.94
6 to 8 p. m.	350	1.006	0.13	0.46	0.7	2.45
Total day	1,140	0.2	2.32	6.42
8 p. m. to 8 a. m.	460	1.017	0.28	1.29	0.75	3.45
Total 24 hours	1,600	3.61	9.87

Phthalein elimination May 10, per cent., first hour 19; second hour 12; two-hour total 31.

Summary: There is slight polyuria during the day as well as at night. Salt output and concentration are both unusually low. Dye excretion is moderately impaired.

CASE 12.—(163670.) Abraham C., aged 14. Previous history, measles and pertussis in early childhood.

Present illness, tertian malaria lasting two weeks in all; no fever after May 8.

Blood: May 16, hemoglobin 60 per cent., erythrocytes 3,700,000.

May 22, incoagulable nitrogen 46 mg. per 100 c.c.; urea nitrogen 32 mg. per 100 c.c.

TABLE 12.—DATA OF RENAL FUNCTION IN CASE 12

May 24, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid— Per Cent. Gm.		Nitrogen— Per Cent. Gm.	
8 to 10 a. m.	35	1.023	0.18	0.06	1.52	0.53
10 to 12 m.	55	1.019	0.46	0.25	1.04	0.57
12 to 2 p. m.	75	1.022	0.76	0.57	0.45	0.34
2 to 4 p. m.	90	1.023	0.49	0.44	1.09	0.98
4 to 6 p. m.	75	1.025	0.47	0.39	1.39	1.04
6 to 8 p. m.	40	1.032	0.27	0.11	1.7	0.68
Total day	370	0.48	1.78	4.14
8 p. m. to 8 a. m.	105	1.022	0.36	0.38	1.03	1.08
Total 24 hours	475	0.45	2.16	5.22

Phthalein elimination, per cent., first hour 48; second hour 20; two-hour total 68.

Summary: Decided retention of water and salt; dye excretion normal.

Comment: During the malarial paroxysm, salt excretion has been found slightly increased, decreased after the fever has begun to decline and increased again immediately after the paroxysm (von Moraczewski: Virchows Arch. f. path. Anat., 1899, 155, 11). The patient, six days after fever, shows decreased salt excretion. There is no sign of a nephritis, although many observers have reported that it occurs frequently after malaria.

CASE 13.—(163331.) Fanny D., aged 15. Past history, repeated attacks of tonsillitis.

Present illness, for three or four weeks, fleeting pains in the joints; right knee and right wrist slightly swollen and a little tender to pressure since the end of April. These symptoms persisted until May 12. The temperature was never above 100 F.

Urine: Single specimens showed albumin, a faint trace usually present; in one of thirteen specimens many granular casts were found.

Blood pressure, systolic 80, diastolic 60.

Blood: May 10, incoagulable nitrogen 42.4 mg. per 100 c.c.; urea nitrogen 9.8 mg. per 100 c.c.

Phthalein elimination, per cent., first hour 13; second hour 33; two-hour total 46.

Summary: The examination was made during the existence of slight fever. The results of the test diet are normal. The salt output as a whole is rather low. Dye excretion is slightly impaired.

CASE 14.—(162439.) Sophie B., aged 34. Past history, married eleven years; five normal pregnancies; no infectious diseases.

Present illness, grippe and tonsillitis beginning February 25. About March 10, legs began to swell. The quantity of urine decreased after that.

Urine: Twenty-Four Hour Specimens:

	Specific Gravity	Albumin	Microscopic	Quantity, c.c.
March 31.....	1.020	Very faint trace	Very few hyaline casts	1,200
April 3.....	1.020	Very faint trace	No casts	1,600
April 9.....	1.020	None	No casts	1,200

Physical examination, March 30, showed edema of eyelids and of legs, which had disappeared before the test diet was given.

Blood pressure: April 4, systolic 140, diastolic 100.

Blood: April 2, incoagulable nitrogen 47 mg. per 100 c.c.; urea nitrogen 12.6 mg. per 100 c.c.

TABLE 13.—DATA OF RENAL FUNCTION IN CASE 14

April 5, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid— Per Cent. Gm.		Nitrogen— Per Cent. Gm.	
8 to 10 a. m.	85	1.012	0.48	0.41	0.74	0.63
12 to 12 a. m.	235	1.007	0.48	1.13	0.35	0.82
12 to 2 p. m.	500	1.006	0.44	2.2	0.29	1.45
2 to 4 p. m.	85	1.015	0.71	0.6	0.81	0.69
4 to 6 p. m.	150	1.013	0.54	0.81	0.58	0.87
6 to 8 p. m.	130	1.013	0.28	0.36	0.66	0.86
Total day	1,185	0.46	5.51	5.32
8 p. m. to 8 a. m.	250	1.024	0.53	1.33	1.36	3.4
Total 24 hours	1,435	0.48	6.84	8.72

Phthalein elimination April 4, per cent., first hour 18; second hour 25; two-hour total 43. March 31, first hour 30; second hour 30; two-hour total 60.

Summary: The result of the test diet is normal. Dye excretion is slightly impaired.

Comment: There is here a definite clinical nephritis following acute tonsillitis and rheumatism. The dye test shows slight impairment. Indeed, by functional tests these kidneys are more nearly normal than those of many of our patients who had clinically only a febrile albuminuria.

CASE 15.—(160926b.) Sidney R., aged 19. Past history, negative.

Present illness, *Staphylococcus aureus* meningitis. Three injections of anti-meningococcus serum were given, the last on Jan. 26, 1916. Temperature range up to 105 F., reached normal March 5.

Urine: Repeated examinations were made of single specimens; specific gravity 1.016 to 1.035. During fever, albuminuria ++; many hyaline and granular casts and a few red blood cells. After February 25, albumin and casts no longer found.

TABLE 14a.—DATA OF RENAL FUNCTION IN CASE 15

March 29, 1916	Quantity, C.c.	Specific Gravity	Sodium Chlorid—		Nitrogen—	
			Per Cent.	Gm.	Per Cent.	Gm.
8 to 10 a. m.	180	1.015	0.68	1.22	0.46	0.59
10 to 12 a. m.	145	1.015	0.94	1.36	0.54	0.78
12 to 2 p. m.	230	1.011	0.53	1.22	0.25	0.57
2 to 4 p. m.	220	1.011	0.57	1.25	0.26	0.57
4 to 6 p. m.	220	1.012	0.77	1.69	0.27	0.59
6 to 8 p. m.	220	1.009	0.48	1.06	0.32	0.7
Total day	1,215	0.64	7.8	3.8
8 p. m. to 8 a. m.	560	1.012	0.63	3.53	0.43	2.41
Total 24 hours	1,775	0.69	11.33	6.21

Phthalein elimination, March 27, per cent., first hour 45; second hour 25; two-hour total 70.

Summary: This patient shows slight fixation of the specific gravity and the quantity of the single specimens; polyuria both during the day and night periods, with low concentration of nitrogen at night. The salt excretion is increased. In spite of the normal dye excretion the whole impression is one of decided functional impairment.

This patient (Case 15) was seen at Montefiore Home and Hospital about a year after the first observations were made. His meningitis had left him paraplegic, but otherwise well. The following examinations were made:

Urine: Repeated examinations were made of the twenty-four hour collection; specific gravity 1.018; quantity, about 1,000 c.c. on house diet; casts and albumin were absent.

Feb. 24, 1917, phthalein elimination, per cent., first hour 8; second hour 20; two-hour total 28.

TABLE 14b.—DATA ON RENAL TEST DIET

April 3, 1917	Quantity, C.c.	Specific Gravity	Sodium Chlorid—		Nitrogen—	
			Per Cent.	Gm.	Per Cent.	Gm.
7 to 9 a. m.	140	1.0205
9 to 11 a. m.	200	1.020
11 to 1 p. m.	175	1.0165
1 to 3 p. m.	140	1.015
3 to 5 p. m.	130	1.016
5 to 7 p. m.	120	1.017
Total day	905	0.71	6.5	0.8	7.0
7 p. m. to 7 a. m.	455	1.020	0.78	3.5	0.8	3.6
Total 24 hours	1,360	10.0	10.9

Mosenthal meals at 7, 11 and 4.

Summary: The changes during the year that has elapsed since the last examination are: the specific gravity shows the same amount of fixation but at a higher level; the total quantity is less; nocturnal polyuria is less marked. Phthalein excretion is now decidedly impaired.

TABLE 15.—SUMMARY

Case No.	Diagnosis	Days after Fever	Amount of Urine Excreted, C.c.		Specific Gravity*		Sodium Chloride Excretion in Urine			Phthalic Excretion in 24 Hrs., per Cent.	Previous History of Infectious Diseases or Nephritis	Urine. Clinical Diagnosis of Renal Lesion
			Total in 24 Hrs.	Night Specimen	Range in 24 Hrs	Night Specimen	Percentage					
							Range for 24 Hrs.	Night Urine				
1	Acute lobar pneumonia	5	910	(115)†	19-31	19	0.62-1.11	0.62	7.7	(11.0)	Febrile albuminuria
2	Acute lobar pneumonia	6	1,040	375	7-24	24	0.25-0.73	0.73	5.4	33.0	Febrile albuminuria
3	Acute lobar pneumonia	8	1,630	(310)	8-17	(17)	0.25-0.74	0.71	8.0	53.0	Slight febrile albuminuria
4	Acute lobar pneumonia	8	1,100	260	12-28	28	0.55-1.03	0.73	8.0	39.5	Scarlet fever	Febrile albuminuria
5	Acute lobar pneumonia	8	1,125	640†	(9-15)	13	0.33-0.64	0.33	5.5	(55.0)	Scarlet fever	Chronic nephritis?
6	Acute lobar pneumonia	11	1,140	(135)	6-18	(16)	0.18-0.53	0.53	5.5	(10.0)	Typhoid fever	Febrile albuminuria
7	Acute pleurisy with effusion	3	1,065	250	11-23	21	0.20-0.59	0.59	4.4	34.0	Tonsillitis	Slight febrile albuminuria
8a	Typhoid fever.....	8	1,155	(420)	10-21	(17)	0.59-0.75	0.51	5.3	27.0	Slight febrile albuminuria
8b	Typhoid fever.....	230	1,205	(440)	26-35	30	0.67-1.62	1.31	16.2	(50.0)	Negative
9	Typhoid fever.....	9	1,470	(440)	(11-19)	(17)	0.34-1.03	0.46	9.0	27.0	Pneumonia	Negative
10	Typhoid fever.....	15	1,790	(580)	5-21	(16)	0.35-0.97	0.82	12.5	(56.0)	Slight febrile albuminuria
11	Typhus.....	3	1,600	(460)	6-17	(17)	0.12-0.47	0.23	3.6	31.0	Negative
12	Malaria.....	5	475	105	19-32	22	0.18-0.70	0.36	2.2	68.0	Measles; pertussis	Slight febrile albuminuria
13	Subacute rheumatism	0†	1,480	260	6-18	18	0.12-0.75	0.60	5.4	(16.0)	Tonsillitis	Febrile albuminuria
14	Tonsillitis; grippe	35	1,435	250	6-24	24	0.28-0.71	0.53	6.8	60.0 (43.0)	Chronic nephritis
15a	Staphylococcus meningitis	23	1,775	(560)	(9-15)	12	0.53-0.94	0.63	11.3	70.0	Chronic nephritis
15b	Staphylococcus meningitis	390	1,365	(455)	(15-21)	20	0.73	10.0	28.0	Chronic nephritis

* The figures mean above 1,000.

† Figures in parentheses = slight impairment; figures in heavy faced type = moderate impairment.

‡ Temperature constantly below 100 F.

Comment: The picture in this patient is in striking contrast to some of the patients with febrile albuminuria. In a number of these the impaired dye excretion was the only sign of kidney damage. Here, however, we have normal dye excretion in a patient who shows unmistakable renal disturbance. Ordinary methods of examination failed to reveal the undoubted chronic nephritis. Examination after the lapse of one year shows moderately impaired dye excretion, with persistence of the impairment in renal function as shown by the test diet. The damage to the kidneys has evidently grown worse.

Thanks are extended to Dr. Alfred Meyer and Dr. Morris Manges for the opportunity, so readily offered, of studying patients in their wards, and to Dr. Lester J. Unger, former house physician, for his valuable and efficient aid in organizing the work in the wards.

254 West Eighty-Second Street.

HEART BLOCK ASSOCIATED WITH HIGH BLOOD PRESSURE *

JOHN H. MUSSER, JR., M.D.

PHILADELPHIA

The following two cases present several instructive phases of cardiovascular disturbance which will be discussed in detail following the case histories.

REPORT OF CASES

CASE 1.—Mrs. G., aged 60; white; housework; born in Ireland; admitted Sept. 28, 1913; discharged Nov. 8, 1913. The patient was admitted with the diagnosis of acute appendicitis. Appendectomy was performed a few hours after admission to the ward and the appendiceal region drained. Recovery was slow and when the patient was discharged there was a persistent, discharging sinus. While in the surgical ward note was made, "heart beats with a very slow rhythm." The patient was discharged from the surgical service Nov. 8, 1913, and readmitted to the medical service Dec. 30, 1913, on account of dizziness, headache and faintness. She had complained of the buzzing in the head for the previous three months with headaches and dizziness, had had frequent dizzy spells, and on two occasions in the previous month she nearly fell to the floor owing to dizziness, but had never lost consciousness. She had had scanty urination with no pain or burning, occasional throbbing in the head, much shortness of breath, palpitation of the heart and slight swelling of the feet but no cough, no vomiting, some nausea and belching of gas, some general abdominal pain. The bowels were constipated. The patient had never fainted.

Examination of the heart showed a slight enlargement down and to the left. The aortic second sound was accentuated; there was a soft blowing systolic murmur at the apex.

The urine excreted while in the hospital varied between 700 and 900 c.c. in the twenty-four hours. The specific gravity in numerous examinations was always high. Traces of albumin and hyaline casts were regularly found. Phenolsulphonephthalein excretion the first hour was 10 per cent., second hour, 7 per cent. The temperature was always normal; the pulse rate varied between 32 and 68 per minute. The blood pressure estimations were as follows:

12/30	270 - 150?	Pulse rate about 40.
1/1	230 - ?	
1/4	230 - 90	
1/7	204 - 118	
1/10	194 - 78	
1/12	182 - 76	

Mrs. G. was seen from time to time after her discharge. She was last visited in November, 1916. At that time the pulse rate was extremely slow (36) and it had been continuously since leaving the hospital. On account of an ignorant prejudice of her husband against mechanical medical instruments, permission had been refused for any type of examination, and I have been unable to take the pressure or make tracings. The same essential conditions, however, were apparently present as when in the hospital. Cardiac compensation was good, but there

* Submitted for publication March 1, 1917.

had evidently developed a certain amount of cerebral softening, as the mentality was decidedly feeble.

CASE 2.—Mrs. W., aged 65; white; occupation, housewife; admitted Sept. 26, 1913; discharged Nov. 7, 1913.

This patient was seen in the medical dispensary, where, in the course of the routine examination, it was found that she had a blood pressure of 270 systolic, 140 diastolic. On account of the cardiovascular condition she was referred to the ward where the following notes were made:

"Shortness of breath on exertion; weakness; cardiac palpitation. Began to have shortness of breath, weakness, and to feel the heart beat about the end of May; cannot do any work or exercise; walking, going upstairs and all such efforts bring about these symptoms; the patient also gets, at times, shooting pains on the left side of the thorax which radiate to the precordia, and to the left shoulder and down the left arm. The symptoms have gradually been getting worse.

"The patient has had general good health, except for the latter part of her life. Had measles, whooping cough, mumps and diphtheria in childhood; was then in good health until four years prior to admission, when she had nervous prostration lasting about two months; began to feel cardiac palpitations after this. These were soon followed by inflammatory (?) rheumatism, polyarticular, lasting about six weeks; the pain reappearing at intervals up to the present. She has had frequent attacks of sore throat, though of mild character.

"The patient's mother died of stroke of paralysis at 53; father died with considerable anasarca at 63; had nine brothers and sisters, eight of whom are dead.

"Married forty-five years; did her own housework till husband's death thirty years prior; after that did outside general housework. Had three children; no miscarriages. Denied the use of alcohol and tobacco.

"*Physical Examination.*—The patient is an old female, well built and preserved. The physical findings are negative except for those of the cardiovascular system.

"Heart: Apex beat; visible in fifth interspace one-half inch to left of the midclavicular line, very irregular and slow in rhythm, and the beat is moderately strong; normal area of dulness; sounds weaker than normal and irregular; no valvular murmurs heard; peripheral arteries show slight thickening; ophthalmoscopic examination showed slight sclerosis of retinal vessels.

"September 28: No apparent change since admittance. Feels comfortable while in bed without exertion. Pulse tracing shows heart block.

"October 1: Slightest exertion seems to stir up the heart to beat more rapidly. Has no difficulty while remaining still.

"October, 7: Blood pressure, 165-75; weight about the same.

"October 31: Nothing indicating extra systoles or blocked beats. Temperature, pulse and respiration normal. General condition good.

"November 7: Condition about the same as last note; no change found. Appears in good condition and has not felt uncomfortable for several weeks."

Laboratory Reports.—Blood: red blood count, 3,630,000; white blood count, 12,100; hemoglobin 62 per cent.; Wassermann, negative.

Urine: In twenty-seven examinations, traces of albumin were found at times, as well as occasional hyaline casts. Excretion varied between 500 and 1,800 c.c.; sp. gr., 1.010 to 1.032.

After four or five days in bed the pulse increased from an average of 48 to 60 beats per minute, to 80 to 100. The blood pressure while in bed during the latter part of the patient's stay in the ward was never over 165 systolic, 125 diastolic. According to the method of Stone her heart showed an overload of 47. The pulse work (Sahli) varied from 7.1 mm. Hg lying down to 14.96 mm. Hg while sitting up. During the interval following discharge from

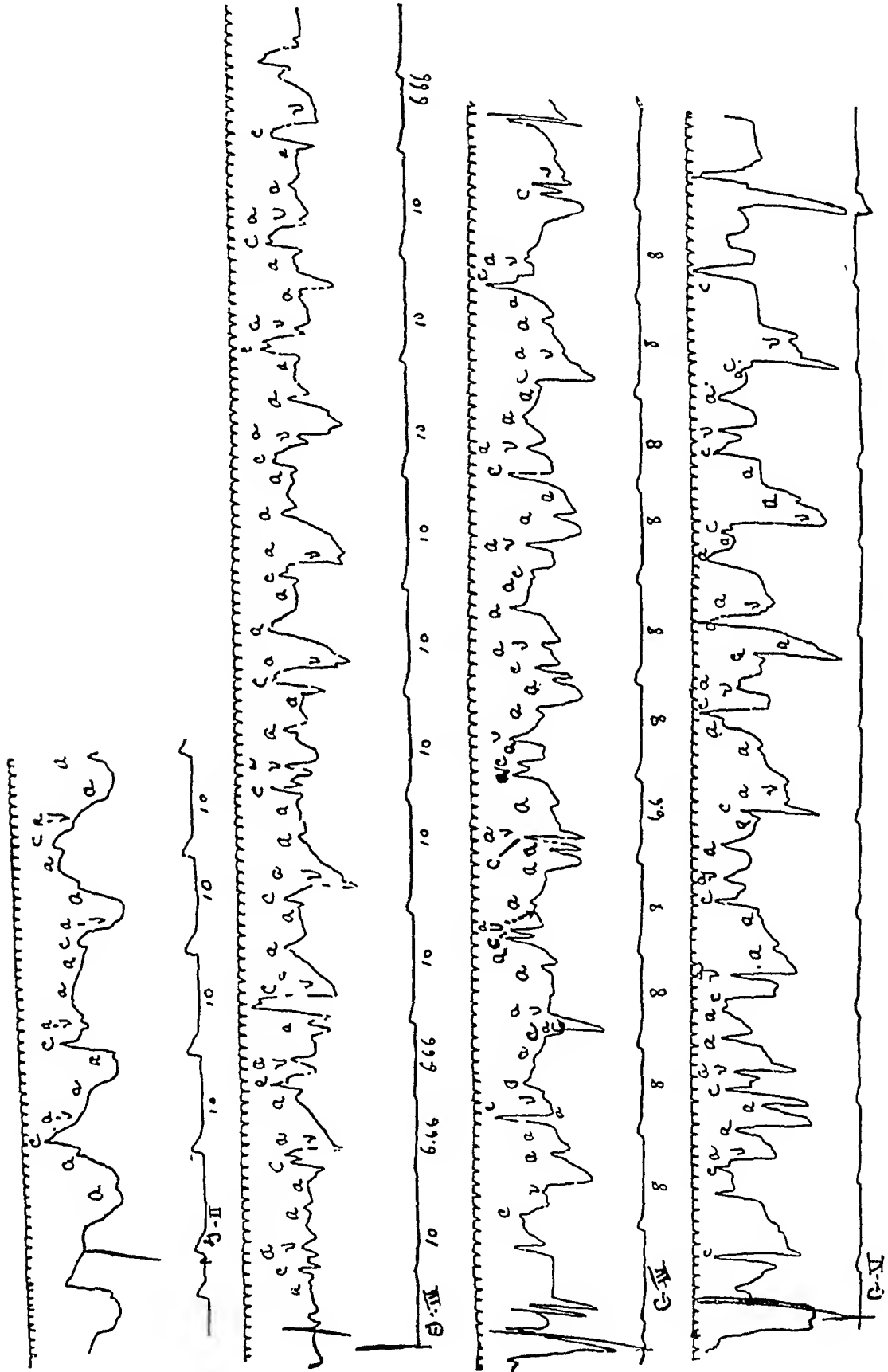


Fig. 1.—Tracings of Mrs. G., taken during stay in Presbyterian Hospital.

the hospital Mrs. W. was in fairly good condition. She was able to do a fair amount of housework without much discomfort. I saw her from time to time and noted that heart rate fell shortly after leaving the hospital and remained persistently low afterward. At my request she was readmitted to the hospital in October, 1916, for further observation. At that time the following notes were made:

"The patient has been suffering from shortness of breath for several years. She becomes very short of breath on slight exertion; walking across the room often forces her to sit down to rest. She has attacks of precordial pain which are brought on by slight exertion. The pain radiates to the shoulder and arm. She is unable to lie flat, but always sleeps propped up by several pillows. At times she has swelling of the ankles. She has had a cough for several years. Each morning she has a coughing spell lasting five or ten minutes. She is bothered very little the rest of the day by the cough. Phlegm accompanies the cough. She has no cardiac palpitation, but, on the contrary, she says at times her heart seems to beat hardly at all. The bowels are regular; appetite good; occasionally has attacks of nausea and vomiting just after eating; no trouble at urination; no nycturia. At times she has a little bearing down pain after urination.

"At the base of the lungs there are fine, moist râles. Heart sounds are clear but very slow and irregular. With the stethoscope on the point of maximum impulse the heart sounds do not correspond with the pulsation over the jugular vein, they being very much faster than the apical pulsations. All the beats heard at the apex come through to the radial. There is a soft systolic murmur over the mitral area. No murmur is heard at the aortic or pulmonary area; heart border—above, third rib; to the left, $1\frac{1}{2}$ in. outside of midclavicular line; to the right, sternal line; aortic second sound accentuated; slight sclerosis of radials; blood pressure, 220-75.

"October, 12: Patient's general condition is good. She has no pain. She walks around the ward a little each day.

"October 17: Condition about the same. She complains of pain about the heart. Blood pressure, 230-65."

Laboratory Reports.—Urine in five examinations showed no casts; a very faint trace of albumin twice; sp. gr., between 1.019 and 1.029.

Blood: Hemoglobin, 60 per cent.; red blood count, 3,980,000; white blood count, 9,900.

The temperature was continuously normal; respirations varied between 24 and 16; the pulse rate was uniformly between 38 and 48, once or twice going over the latter figure.

GRAPHIC EVIDENCES OF HEART-BLOCK

The polygraphic tracings of Mrs. G. will first be discussed. G-II, taken on admission to the ward, shows a 3:1 block. As G-III shows more clearly than G-II the sequence of events, and as the two tracings illustrate the same condition, the former alone will be discussed. This tracing was taken preliminary to an injection of atropin. It can be noted in the tracing of the radial artery that each ventricular systole for the most part occurs two seconds after the preceding one. Occasionally, however, an impulse comes through from the auricle which causes a corresponding contraction of the ventricle. These ventricular systoles, when they occur, are 1.33 seconds apart and are due to the temporary change of a 3:1 to a 2:1 block. The jugular tracing shows,

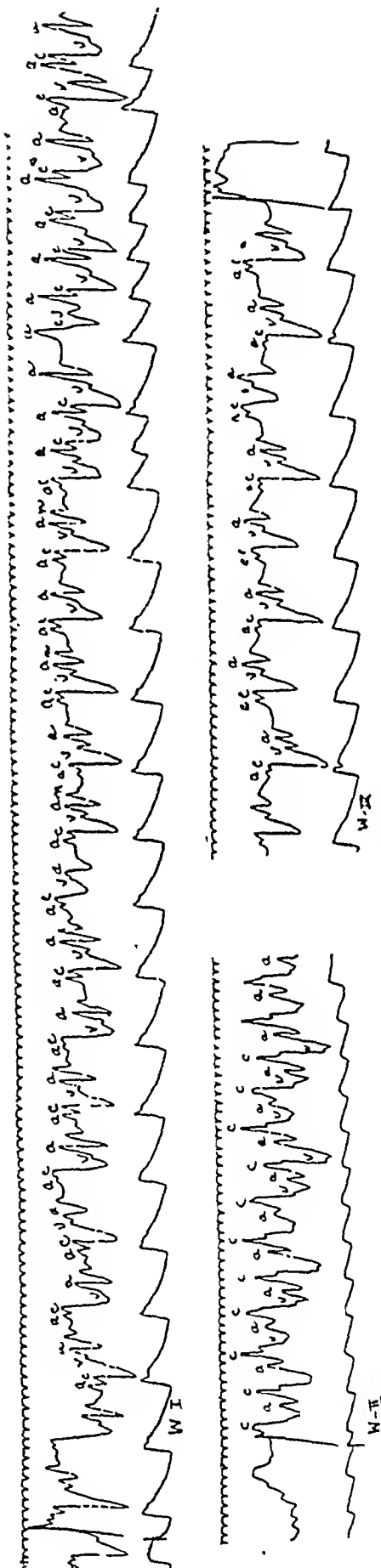


Fig. 2.—Tracings of Mrs. W., taken in Presbyterian Hospital.

except where the extra ventricular beats occur, a regularly recurring series of *a* waves which are 0.66 of a second apart. The first *a* wave is not followed by ventricular response; the second *a* wave is followed by the usual *c* and *v* waves; a third *a* wave occurs synchronously with the *v* wave. The evidence that such synchronism takes place is based on the fact that the distance each *a* wave is from the next is equivalent to the distance from *a* to *v* to *a*; furthermore, the time interval between each ventricular response is two seconds, excepting where the additional beats appear, due to change in the rate of block to 2:1, when it is 1.33 seconds. If the rhythm were a 2:1 rhythm rather than a 3:1 rhythm, then the interval of this additional ventricular response would be exactly one second. Likewise, it would seem to be unlikely that a 2:1 rhythm is present, because the auricle would then contract twice at a rate of approximately 90 per minute, after which there would be a pause followed by another series of two beats. Such a condition is possible but improbable, and necessitates the assumption of a 2:3 sino-auricular block, as well. The auricles may contract irregularly when there is abnormal vagus irritability; for example, sinus arrhythmia, when extra systoles arise in the sinus or the auricle, when there is sino-auricular block and when there is auricular fibrillation; but none of these conditions is suggested in the tracing. Sinus arrhythmia, sinus or auricular extra systoles and auricular fibrillation can be ruled out at once, although a sino-auricular block might possibly be present; but as such a condition is rare, it seems fair to hold that the third auricular contraction occurs at the same time as the ventricular.

The next tracing, G-IV, illustrates a tracing taken ten minutes after the hypodermic injection of 0.2 mg. atropin sulphate. The same sequence of events takes place, except that the auricular, and consequently the ventricular, rate is more rapid as a result of the suppression of the inhibitory effect of the vagus by the atropin.

G-V is a tracing taken twenty minutes later. Again the same sequence of events occurs. In both the tracings taken after atropin was injected, there is no essential change in the character of the block, showing it to be organic rather than functional in type.

The graphic studies of Mrs. W. include not only polygrams, but also electrocardiograms. The tracing, W-I, taken in 1913, is presented as a long strip in order to show towards the end of the tracing a few contractions that arise as a result of impulses coming through without blocking in the bundle of His. Here the phlebogram shows a normal tracing. Elsewhere an additional *a* wave is shown which is followed by an extra wave (*n*) the genesis of which I have been unable to determine and which may be an artefact due to instrumental "fling." The tracing then shows a partial (2:1) block with occasional periods when

beats get through normally. It is interesting to note the differences in size of the arteriogram waves where there is block and where the block has disappeared. The waves are almost twice as large when the rate is slow as compared with the heart beats when twice as rapid, demonstrating that when all other factors are equal, the adjustment of levers

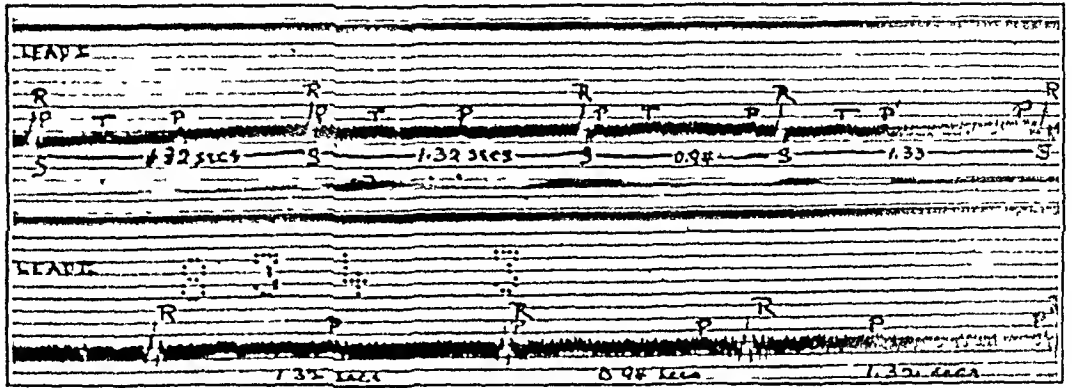


Fig. 3.—Electrocardiogram of Mrs. W., taken Sept. 14, 1916. Leads I and III.

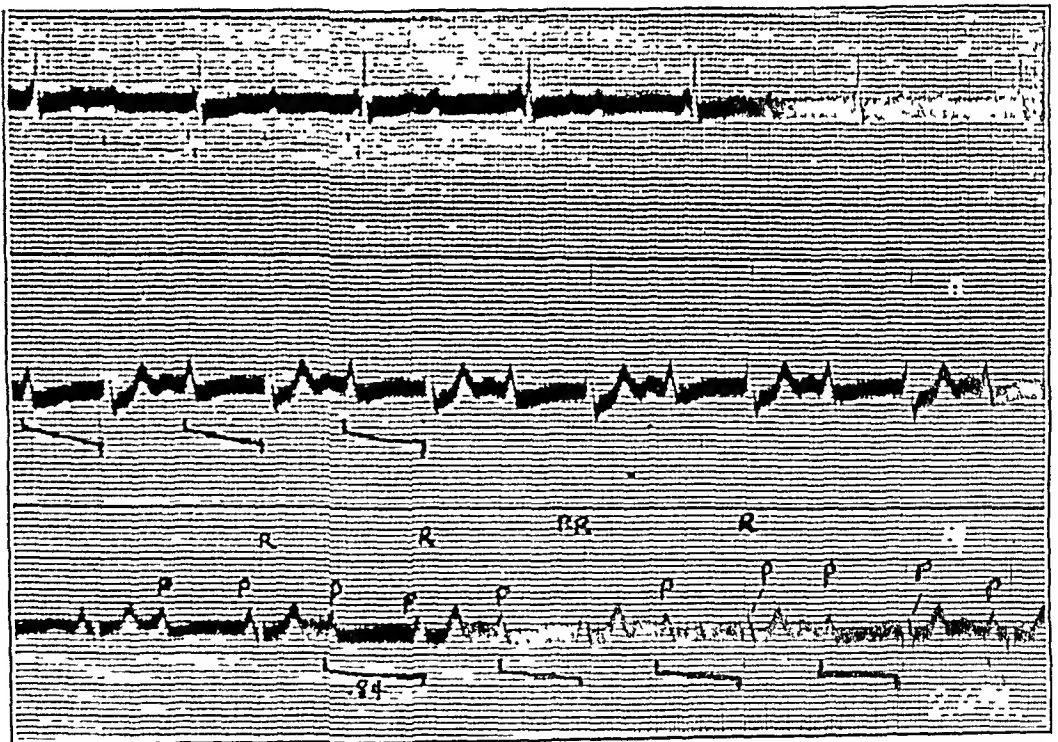


Fig. 4.—Electrocardiogram of Mrs. W., taken Oct. 10, 1916

being unchanged, a high pressure, presumably, causes large graphic arterial waves. Tracing W-III was taken two days after admission to the ward and following an injection of 0.3 mg. of atropin. There is no essential or minor change in the tracing as compared with the part of W-I that shows 2:1 block. Tracing W-II was taken two weeks

after rest in bed. Here a practically normal tracing is shown, except that there is possibly a slight prolongation of the a-c interval. The first electrocardiogram, Lead 1, taken September, 1916, shows partial heart block. The ventricular complex occurs every 1.32 seconds, the

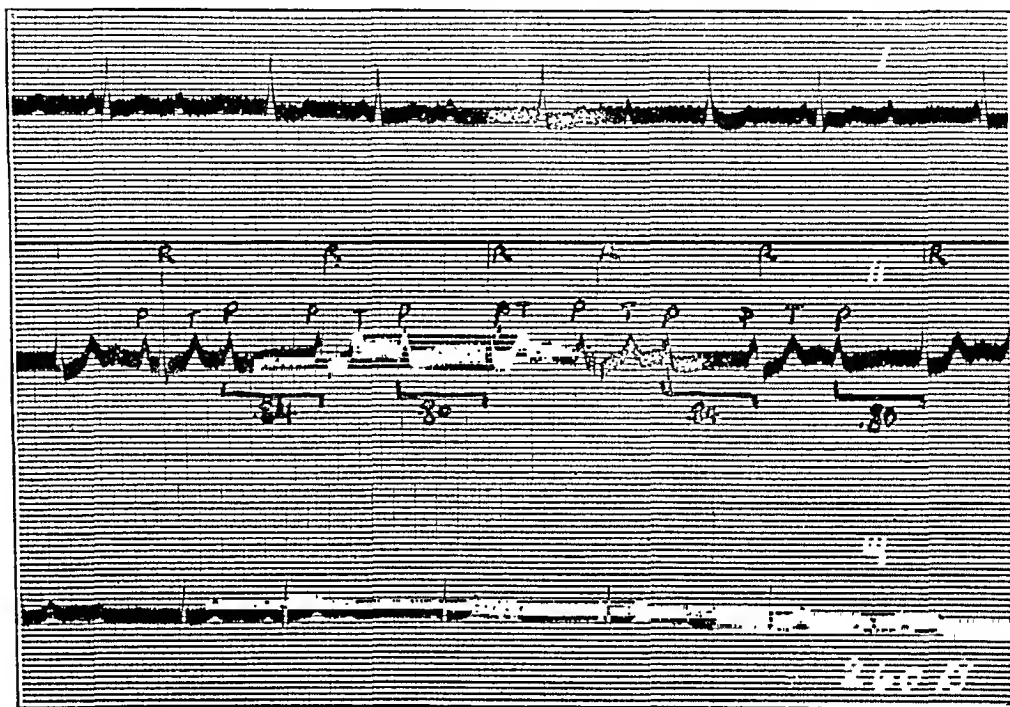


Fig 5.—Electrocardiogram of Mrs. W., taken Oct. 12, 1916.

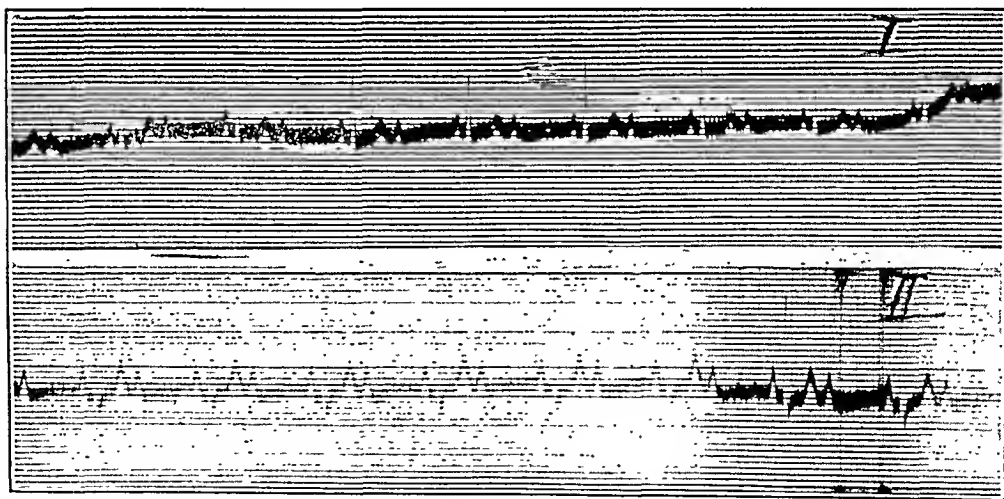


Fig. 6.—Electrocardiogram of Mrs. W., taken Oct. 23, 1916. Lead III not entirely clean and hence not reproduced.

auricular every 0.66 second, in the periods of 2:1 block. The P waves show a complex relationship to the R S T group, caused by the fact that the partial block varies at irregular intervals between a 2:1 and a 3:2 grade. The short cycles represent the 3:2 block, the longer cycles

the 2:1 block. The P-R intervals are greatly prolonged and vary according to the degree of refractility that exists at the moment in the junctional tissues. Tracings 260 A and B were taken one month later. Here the ventricular rate is 1.45 seconds, or approximately 42 per minute. Here again there is partial dissociation, with the block varying between a 2:1 and a 3:2 rhythm with a P-R interval that is 0.84 second long at times (see 260-B, Lead II). Tracings 264 and 267, taken thirteen and fifteen days later, respectively, show a clear 2:1 block with a normal P-R interval; 260-A shows a 2:1 rhythm, where every other P falls exactly or almost on the R of the preceding cycle. In Lead II the cycles are constant. In Lead III in the first cycle P is

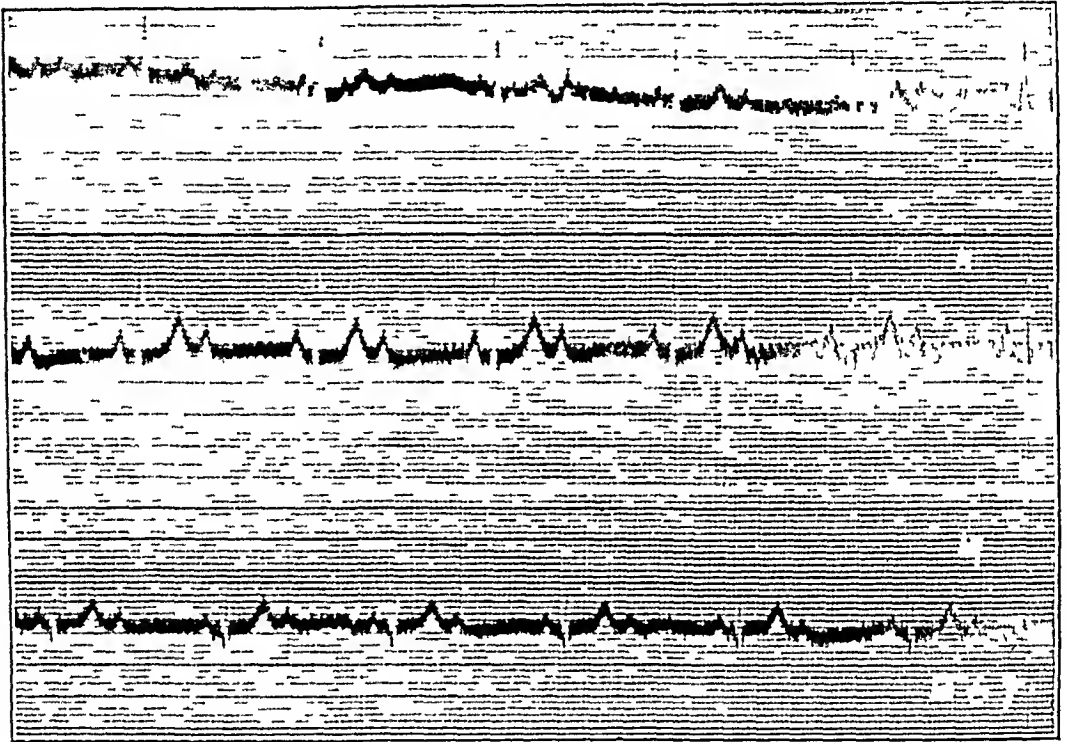


Fig. 7.—Electrocardiogram of Mrs. W., taken Oct. 25, 1916.

0.19 of a second from R, but with each cycle, gets nearer, then merges (note the higher R wave), then appears on the down stroke; conductivity improves gradually until the last cycle shows *no* block. In Lead I, the second P hovers about R, at first receding from it, then approaching, till in the last cycle it is merged.

From the evidence here presented the two patients unquestionably had heart block. The first showed but little change in the character of the block at any time. The several tracings taken of patient, Mrs. W., showed variations from a normal tracing to different degrees of partial block, at times associated with an extremely prolonged P-R interval.¹

1. Thayer: THE ARCHIVES INT. MED., 1916, **17**, 13.

BLOOD PRESSURE FINDINGS

The most interesting determination in these two cases was the extremely high systolic pressure. In both of them the pressure during the block and before rest in bed was higher than the Nicholson sphygmomanometer can register. In reviewing the literature² of heart block from 1904 to 1916, I was able to find cases of heart block associated with high systolic pressure reported by Bramwell (systolic pressure 235), Falconer (systolic pressure 230 during attacks), Gibbes and Dally (systolic pressure 240-Pachon), Gibson (pressure of 270), Gossage (pressure 200-220), Griffith and Kennedy (systolic pressure as high as 260), Grosh (pressure 225), Herrick (two cases, systolic pressure 240 and 200, respectively), Hoffman (two cases, pressure of 240 and 250, respectively), Hume (systolic pressure 230), Jellinek and Cooper (two cases with pressures over 200), Levine (systolic pressure 196), Purser and Davis (systolic pressure 214 during attack, 180 in the interval), Schwarzmamm (systolic pressure 235), Souques and Routier (two cases, systolic pressure 250 and 220, respectively). In none of these cases did the systolic pressure approach closely the pressure in the two cases detailed above. The pressure of these two patients was first taken after they had been doing a certain amount of work. After rest in bed the pressure of both fell very materially; in Mrs. G's case about 100 mm. Hg; in Mrs. W's case somewhat more. When the block disappeared in the latter patient's case after rest in bed, the systolic pressure never exceeded 155, though the diastolic pressure remained high. These figures of 155-125 probably represent the true pressure without relation to the block, as they were found only when the block disappeared. Although the block returned shortly after the first stay of Mrs. W. in the ward, nevertheless, the possible dangers of the extremely high pressure having been fully explained to her, she so altered her manner of living that she took no violent, sudden or continuous exertion of any kind, and made no severe demand on the heart. Her pressure, even with the block present under these circumstances, never attained the heights reached on the first examination, which was made after resting a short time from a long walk.

Both of these patients were obviously cases of cardiosclerosis with associated fibrotic changes in the bundle of His. The first patient had apparently comparatively slight peripheral sclerosis, if we may judge from the low diastolic pressure. The second apparently had considerable peripheral resistance, as her diastolic pressure remained consistently high. In this patient the sclerotic changes evidently are progressing steadily, as the block no longer disappears after rest in bed.

2. References to the literature will be found alphabetically arranged at the end of the article.

BLOOD PRESSURE FINDINGS

The most interesting determination in these two cases was the extremely high systolic pressure. In both of them the pressure during the block and before rest in bed was higher than the Nicholson sphygmomanometer can register. In reviewing the literature² of heart block from 1904 to 1916, I was able to find cases of heart block associated with high systolic pressure reported by Bramwell (systolic pressure 235), Falconer (systolic pressure 230 during attacks), Gibbes and Dally (systolic pressure 240-Pachon), Gibson (pressure of 270), Gossage (pressure 200-220), Griffith and Kennedy (systolic pressure as high as 260), Grosh (pressure 225), Herrick (two cases, systolic pressure 240 and 200, respectively), Hoffman (two cases, pressure of 240 and 250, respectively), Hume (systolic pressure 230), Jellinek and Cooper (two cases with pressures over 200), Levine (systolic pressure 196), Purser and Davis (systolic pressure 214 during attack, 180 in the interval), Schwarzmänn (systolic pressure 235), Souques and Routier (two cases, systolic pressure 250 and 220, respectively). In none of these cases did the systolic pressure approach closely the pressure in the two cases detailed above. The pressure of these two patients was first taken after they had been doing a certain amount of work. After rest in bed the pressure of both fell very materially; in Mrs. G's case about 100 mm. Hg; in Mrs. W's case somewhat more. When the block disappeared in the latter patient's case after rest in bed, the systolic pressure never exceeded 155, though the diastolic pressure remained high. These figures of 155-125 probably represent the true pressure without relation to the block, as they were found only when the block disappeared. Although the block returned shortly after the first stay of Mrs. W. in the ward, nevertheless, the possible dangers of the extremely high pressure having been fully explained to her, she so altered her manner of living that she took no violent, sudden or continuous exertion of any kind, and made no severe demand on the heart. Her pressure, even with the block present under these circumstances, never attained the heights reached on the first examination, which was made after resting a short time from a long walk.

Both of these patients were obviously cases of cardiosclerosis with associated fibrotic changes in the bundle of His. The first patient had apparently comparatively slight peripheral sclerosis, if we may judge from the low diastolic pressure. The second apparently had considerable peripheral resistance, as her diastolic pressure remained consistently high. In this patient the sclerotic changes evidently are progressing steadily, as the block no longer disappears after rest in bed.

2. References to the literature will be found alphabetically arranged at the end of the article.

Probably one of the most instructive points demonstrated in the study of these two cases is the relationship of extremely high blood pressure to the cardiac strength and complete filling of the ventricle. The systolic pressure represents the strength of the heart beat, and is dependent largely on the diastolic filling of the ventricles and the completeness of systolic emptying. In these two patients the pressure was raised very markedly; there were the factors of complete filling of the ventricle as a result of the very slow ventricular rate which Henderson believes increases the amplitude of the systolic discharge, and also the fact that with each beat the ventricle was filled by the extra auricular beats with more blood than it would receive under ordinary circumstances, though Wiggers³ does not believe that auricular systoles aid materially in filling the ventricle. Furthermore, a ventricle in low tone has a greater systolic output than one of high tone, provided it is not fatigued and dilated, but is able to expel all the blood — to empty itself completely with each systole.

The complete filling of the ventricle had apparently a very distinct effect on the pressure, because on the one individual whose block disappeared, in spite of the cardiac hypertrophy, systolic pressure fell some 100 mm. Hg when the block was abolished. In other words, the very high systolic pressure apparently depended not so much on the strength of the heart muscle, but on the very complete filling of the ventricle with subsequent contraction on a large mass of blood. This has been shown by physiologic experiments; an increased systolic output causes a rise in systolic and diastolic pressure, provided the pulse rate and peripheral resistance remain constant. On a similar basis can be explained the extremely high pressures associated with aortic insufficiency. The left ventricle contains much more blood than normal, owing to the regurgitation of the blood backward into its chambers. As a result of this the ventricle is enabled to contract with the maximum amount of strength on a large amount of blood, resulting in a high systolic pressure. In both disorders, aortic regurgitation and heart block as here shown, there is, of course, the added factor of the cardiac hypertrophy, but in cardiac hypertrophy unassociated with these lesions, very high pressure is the exception, though relatively high values occur. It is by the forcing out of the larger volumes of blood with each ventricular contraction into the arterial tree that the pressure is raised so markedly, rather than by the ventricular hypertrophy per se. This latter condition is common where pure aortic obstruction exists, but the systolic pressure is usually only slightly elevated despite the hypertrophy, and the frequently associated arteriosclerotic changes. In

3. Wiggers: *Circulation in Health and Disease*. Lea and Febiger, Philadelphia and New York, 1915, p. 68.

the tracing W-1 the difference in the size of the pulse waves when the ventricle is not so completely filled, is graphically shown.

SUMMARY

Two cases of heart block with extremely high systolic pressure are recorded. Evidence is offered to show that this high pressure is dependent more on increased blood mass discharged by the left ventricle than on the associated cardiac hypertrophy and peripheral sclerosis.

REFERENCES

- Allan, G. A.: Case of Complete Auriculoventricular Heart Block, *Brit. Med. Jour.*, 1914, **1**, 1186.
- Allen, H. W.: The Occurrence of Heart Block in Acute Disease, *California State Jour. Med.*, 1915, **13**, 310.
- Armstrong and Mönckeberg: Herzblock, bedingt durch primären Herztumor, *Deutsch. Arch. f. klin. Med.*, 1911, **102**, 144.
- Arndt, J.: Perpetuierliches Vorhofflimmern bei permanenter Kammerautomatie, *Ztschr. f. klin. Med.*, 1913, **78**, 526.
- Askenstedt, F. C.: Heart Block, *Kentucky Med. Jour.*, December, 1910.
- Ashton, T. G., Norris, G. W., and Lavenson, R. S.: Adams-Stokes Disease Due to a Gumma in the Interventricular Septum, *Am. Jour. Med. Sc.*, 1907, **133**, 28.
- Aschoff, Mackenzie, Erlanger, Gibson and Morrow: Some Aspects of Heart Block, *Brit. Med. Jour.*, 1906, **2**, 1103.
- Bachmann, G.: Physiologico-Pathologic Study of Case of Heart Block Occurring in a Dog As a Result of Natural Causes, *Jour. Exper. Med.*, 1912, **16**, 25.
- Barié, E.: Syndrome de Stokes-Adams avec rythme couplé, *Arch. d. mal. du coeur*, 1909, **2**, 65.
- Barié et Cléret: Syndrome de Stokes-Adams a crises paroxystiques avec rythme bicouplé, *Arch. d. mal. du coeur*, 1910, **3**, 209.
- Barr, James: Case of Stokes-Adams Disease, *Brit. Med. Jour.*, 1906, **2**, 1122.
- Beards, C.: Case Showing the Stokes-Adams Phenomena, *Brit. Med. Jour.*, 1907, **2**, 1039.
- Beck and Stokes: Case of Diffuse, Purulent, Ventriculoseptal Myocarditis with Adams-Stokes Syndrome, *Jour. Am. Med. Assn.*, 1910, **54**, 1067.
- Beck and Stokes: Clinical and Pathologic Study of a Case of Adams-Stokes Disease, *THE ARCHIVES INT. MED.*, 1908, **2**, 277.
- Beeson, C. F.: Heart Block at Ninety-One Years, *Jour. Am. Med. Assn.*, 1908, **50**, 88.
- Benedict, A. L.: Triple Rhythm Heart Block with Auricular Interruption, *New York Med. Jour.*, 1911, **94**, 484.
- Bishop, L. F.: Adams-Stokes Disease with Complete Heart Block, *Am. Jour. Med. Sc.*, 1910, **139**, 62.
- Bramwell, B.: Remarkable (Temporary) Condition of Pulse in Two Cases of Adams-Stokes Disease with Heart Block, *Edinburgh Med. Jour.*, 1915, **45**, 168.
- Bramwell, B.: Heart Block with Fibrous Degeneration and Partial Obliteration of the Bundle of His, *Brit. Med. Jour.*, 1909, **1**, 995.
- Bridgman and King: Case of Heart Block; Recovery, *Bull. Johns Hopkins Hosp.*, 1915, **26**, 412.
- Butler, G. R.: Heart Block (Adams-Stokes Disease), *Am. Jour. Med. Sc.*, 1907, **133**, 715.
- Butterfield, H. G.: Acute Carditis and Heart Block, *Heart*, 1912, **3**, 203.

Christian, H. A.: Transient Auriculoventricular Dissociation with Varying Ventricular Complexes Caused by Digitalis. *THE ARCHIVES INT. MED.*, 1915, **16**, 341.

Clarac and Pezzi: Les signes d'auscultation de la dissociation auriculo-ventriculaire. *Presse méd.*, Aug. 1, 1914, p. 590.

Clayton, T. A.: More Common Forms of Cardiac Irregularity with Report of Case of Heart Block. *Am. Jour. Med. Sc.*, 1912, **144**, 697.

Coffen, T. H.: Digitalis Heart Block. *Northwest Med.*, 1914, **6**, 334.

Cohn, A. E.: A Case of Transient Complete Auriculoventricular Dissociation, Showing Constantly Varying Ventricular Complexes. *Heart*, 1913, **5**, 5.

Cohn and Fraser: The Occurrence of Auricular Contractions In a Case of Incomplete and Complete Heart Block, Due to Stimuli Received from the Contracting Ventricle. *Heart*, 1914, **5**, 141.

Cohn and Lewis: Auricular Fibrillation and Complete Heart Block. A Description of a Case of Stokes-Adams Syndrome, Including the Postmortem Examination. *Heart*, 1912, **4**, 15.

Cohn and Lewis: Report of a Case of Transient Attacks of Heart Block, Including a Postmortem Examination. *Heart*, 1911, **2**, 241.

Cohn and Lewis: A Description of a Case of Complete Heart Block, Including the Postmortem Examination. *Heart*, 1912, **4**, 7.

Coombs, C.: Example of Adams-Stokes Syndrome. *Bristol Med.-Chir. Jour.*, 1913, **31**, 30.

Cotton, E.: Bradycardies permanentes d'origine organique et d'origine inorganique: déblocage par l'atropine. *Arch. d. mal. d. cœur*, 1915, **8**, 149.

Cowan, Fleming and Kennedy: Heart Block and Nodal Rhythm in Acute Infections. *Lancet*, London, 1912, **1**, 277.

Danielopolu, D.: Sur la dissociation sino-auriculaire. *Arch. d. mal. du cœur*, 1913, **6**, 792.

Dessert, P. T.: Case of Stokes-Adams Disease. *U. S. Naval Bull.*, 1907, **1**, 39.

d'Espine and Coltin: Bradycardia vraie par dissociation totale auriculo-ventriculaire. *Bull. de l'Acad. de méd.*, Paris, 1915, **74**, 285.

Dykes, A. L.: Temporary Partial Heart Block Occurring as Sequel to Acute Pneumonia. *Lancet*, London, 1912, **2**, 1008.

Earnshaw, H.: Adams-Stokes Syndrome of Prolonged Duration, Ending in Apparent Recovery. *Am. Jour. Med. Sc.*, 1910, **139**, 503.

Emanuel, J. G.: On a Case of Heart Block. *Lancet*, London, 1910, **1**, 856.

Erlanger and Blackman: Further Studies in the Physiology of Heart Block in Mammals. *Heart*, 1909, **1**, 177.

Eyster and Evans: Sino-Auricular Heart Block, Report of Case in Man. *THE ARCHIVES INT. MED.*, 1915, **16**, 832.

Fallén, F. C.: Heart Block. *St. Louis Med. Rev.*, March 9, 1907, p. 237.

Fahr: Ueber die muskuläre Verbindung zwischen Vorhof und Ventrikel im normalen Herzen und beim Adams-Stokes'schen Symptomkomplex. *Virchows Arch. f. path. Anat.*, 1907, **188**, 562.

Falconer, A. W.: Case of Heart Block Showing Large Auricular Waves in Femoral Tracing. *Lancet*, London, 1916, **1**, 865.

Falconer, J. L.: Case of Stokes-Adams Disease. *Brit. Med. Jour.*, 1912, **2**, 1704.

Falconer and Dean: Observations in a Case of Heart Block Associated with Intermittent Attacks of Auricular Fibrillation. *Heart*, 1912, **3**, 247.

Fleming and Kennedy: A Case of Complete Heart Block in Diphtheria with an Account of Postmortem Findings. *Heart*, 1910, **2**, 77.

Foley, T. J.: Stokes-Adams Syndrome. *Boston Med. and Surg. Jour.*, 1905, **153**, 235.

Frank, P.: Adams-Stokes Disease. *Jour. Am. Med. Assn.*, 1912, **59**, 2145.

Fredericq, L.: Dissociation par compression graduée des voies mortices et arrestatrices contenues dans le faisceau de His. *Arch. Internat. d. physiol.*, 1912, **11**, 405.

Fuchs, H.: Ueberleitungsstörung im Verlauf der Salvarsanbehandlung bei später Sekundärlues, München. med. Wchnschr., 1913, **60**, 2339.

Fulton, Judson and Norris: Congenital Heart Block Occurring in a Father and Two Children, Am. Jour. Med. Sc., 1910, **140**, 339.

Gage, I. B.: Heart Block or Adams-Stokes Disease; Report of a Case, Maine Med. Assn. Jour., 1915, **5**, 431.

Gallavardin, L.: Trois cas de Stokes-Adams avec block total, Lyon méd., 1911, **117**, 1341.

Gallavardin, L.: Du block partiel et toléré, Lyon méd., 1911, **116**, 653.

Gallavardin, L.: Du syndrome de Stokes-Adams, Lyon méd., 1910, **115**, 626.

Gallavardin, L.: Pausas ventriculaires et accidents vertigineux dans la maladie de Stokes-Adams, Lyon méd., Jan. 4, 1914, p. 3.

Gallavardin, L.: Altération du complexe ventriculaire électrique (block total ou block partiel), Arch. d. mal. du cœur, 1914, **7**, 313.

Gallavardin, L.: Contractions auriculaires perceptibles à l'oreille dans le block total, Arch. d. mal. du cœur, 1914, **7**, 171.

Gallavardin and Croisier: Tachycardie paroxystique par block partiel. Les rapports avec l'arythmia complète, Arch. d. mal. du cœur, 1912, **5**, 433.

Gallavardin and Pallasse: Bradycardie par block partiel au cours d'une crise de rhumatisme articulaire aigu, Arch. d. mal. du cœur, 1914, **7**, 310.

Galloway and Fenton: Royal Society of Medicine, Lancet, London, 1910, **2**, 1762.

Gaither, J. G.: The Stokes-Adams Syndrome, Southern Med. Jour., 1912, **5**, 7.

Gerhardt, D.: Klinische und anatomische Beiträge über Adams-Stokes'sche Krankheit mit Vagusbradykardie, Deutsch. Arch. f. klin. Med., 1912, **106**, 462.

Gerhardt, D.: Rückbildung des Adams-Stokes'sche Symptomenkomplexes. Deutsch. Arch. f. klin. Med., 1908, **93**, 485.

Gesell, R. A.: Cardiodynamics in Heart Block as Affected by Auricular Systole, Auricular Fibrillation, and Stimulation of Vagus Nerve, Am. Jour. Physiol., 1916, **40**, 267.

Gibbes and Dally: Electrocardiogram in Complete Heart Block, Clin. Jour., 1912, **11**, 311.

Gibson, G. A.: Electromotive Changes in Heart Block, Brit. Med. Jour., 1906, **2**, 22.

Gibson and Ritchie: Further Observations on Heart Block, Practitioner, London, May, 1907, p. 589.

Gill, J. M.: Heart Block in Acute Rheumatism, Australasian Med. Gaz., July, 1908, p. 63.

Gill, J. M.: Case of Congenital Heart Block, Australasian Med. Gaz., June, 1911, p. 324.

Goodhart, J. F.: Central Origin of Some Cases of So-Called Heart Block, Lancet, London, 1910, **2**, 792.

Gordinier, H. C.: The Adams-Stokes Disease, Albany Med. Ann., 1906, **27**, 385.

Gordon, H. S.: The Adams-Stokes Syndrome, with Report of Two Cases, Calif. State Jour. Med., 1905, **3**, 210.

Gossage, A. M.: Complete Heart Block, Quart. Jour. Med., 1908, **2**, 19.

Gossage, A. M.: Independent Ventricular Rhythm: Heart Block and the Stokes-Adams Syndrome with Affection of Conductivity, Heart, 1909, **1**, 283. Aged 71; blood pressure 200-220.

Gosse, A. H.: Case of Acute Rheumatic Heart Block, Brit. Med. Jour., 1914, **1**, 1347.

Greuve, J. E.: Heart Irregularities, Auricular Fibrillation, Heart Block, Lancet-Clinic, 1915, **113**, 5.

Griffith, T. W.: Remarks on Two Cases of Heart Block, Heart, 1912, **3**, 140.

Griffith and Kennedy: Case of Complete Auriculoventricular Heart Block, Brit. Med. Jour., 1913, **1**, 1203. Blood pressure as high as 260; patient aged 81.

- Griffith and Kennedy: Supplementary Note on a Case of Heart Block, *Heart*, 1915, **6**, 37.
- Grosh, L. C.: Two Cases of Heart Block, *Ohio State Med. Jour.*, February, 1911, p. 55.
- Handwerck, C.: Adams-Stokes'scher Symptomkomplex: Gumma des Vorhofsseptum, *München. med. Wchnschr.*, 1909, **56**, 916.
- Hart, T. S.: Functional Heart Block; Report of Three Cases, *Am. Jour. Med. Sc.*, 1915, **149**, 62.
- Hay, J.: Stokes-Adams Disease; Report of a Case, *Liverpool Med.-Chir. Jour.*, July, 1906, p. 66.
- Hecht, A. F.: Die Unterscheidung des funktionellen und des organischen Herzblocks, *Ztschr. f. kinderh.*, 1912, **4**, 546.
- Heineke, Muller and v. Hösslin: Zur Kasuistik und des Adams-Stokes'schen symptomkomplexes und der Ueberleitungsstörungen, *Deutsch. Arch. f. klin. Med.*, 1908, **93**, 459.
- Heitz, J.: Les dissociations auriculoventriculaires, *Arch. d. mal. du cœur*, 1910, **9**, 65.
- Held, I. W.: Heart Block, *New York Med. Jour.*, 1913, **97**, 763.
- Herrick, W. W.: Clinical Observations in Heart Block, *Am. Jour. Med. Sc.*, 1910, **139**, 246.
- Herzheimer and Kohl: Der Adams-Stokes'sche Symptomenkomplex und das His'sche atrioventrikulärbündel, *Deutsch. Arch. f. klin. Med.*, 1910, **98**, 330.
- Hewlett, A. W.: Heart Block in the Ventricular Wall, *THE ARCHIVES INT. MED.*, 1908, **2**, 138.
- Hewlett, A. W.: The Blocking of Auricular Extrasystoles, *Jour. Am. Med. Assn.*, 1907, **43**, 1597.
- Hewlett, A. W.: Digitalis Heart Block, *Jour. Am. Med. Assn.*, 1907, **48**, 47.
- Hirschfelder, A. D.: Inspection of the Jugular Vein; Its Value and Limitations in Functional Diagnosis, *Jour. Am. Med. Assn.*, 1907, **48**, 1105.
- Von Hoesslin, H.: Ein Fall von Ueberleitungstörung, bedingt durch Vagusreiz, *Zentralbl. f. inn. Med.*, 1913, **34**.
- Hoffman, A.: Zur Kenntnis des Morgagni-Adams-Stokes'schen Symptomenkomplexes und seiner Differenzierung im Elektrokardiogramm, *Deutsch. Arch. f. klin. Med.*, 1910, **100**, 172.
- Huismans, L.: Ueber Bradykardie und den Stokes-Adams'schen Symptomenkomplex, *München. med. Wchnschr.*, 1909, **56**, 552.
- Hume, W. E.: A Case of Heart Block in Which There Was No Pathologic Lesion of the Connecting Muscular System, *Heart*, 1914, **5**, 149.
- Jagic, N.: Ein Beitrag zur Kasuistik des Adams-Stokes'schen Symptomenkomplexes, *Ztschr. f. klin. Med.*, 1908, **66**, 183.
- Jellick, Cooper and Ophüls: The Adams-Stokes Syndrome and The Bundle of His, *Jour. Am. Med. Assn.*, 1906, **46**, 955.
- Jellinek and Cooper: Report of Six Cases of Heart Block with Tracings and One Postmortem Examination of the Heart, *Brit. Med. Jour.*, 1908, **1**, 797.
- Joachim, G.: Weitere Beiträge zur Frage der Leitungsstörung im Herzmuskel, *Deutsch. Arch. f. klin. Med.*, 1907, **88**, 574.
- Karcher and Schaffner: Ein Fall von Adams-Stokes'schen Krankheit mit Schweile im His'schen Bündel, *Berl. klin. Wchnschr.*, 1908, **45**, 1266.
- Kennedy, A. M.: Auricular-Ventricular Node and Bundle in Case of Adams-Stokes Syndrome, *Glasgow Med. Jour.*, 1912, **77**, 187.
- Kidd, P.: A Case of Adams-Stokes Disease, *Lancet*, London, 1904, **1**, 411.
- Koetzle: Herzblock und Herzschuss, *München. med. Wchnschr.*, 1914, **61**, 2064.
- Krumbhaar, E. B.: Adams-Stokes Syndrome with Complete Heart Block, Without Destruction of the Bundle of His, *THE ARCHIVES INT. MED.*, 1910, **5**, 583.
- Krumbhaar, E. B.: Pathologic Study of Two Cases of Heart Block with Adams-Stokes Syndrome, *THE ARCHIVES INT. MED.*, 1914, **13**, 390.

- Krumbhaar, E. B.: Growth of Our Knowledge of Adams-Stokes Disease, Univ. Pennsylvania Med. Bull., November, 1908, p. 278.
- Laslett, E. E.: A Case Exhibiting the Adams-Stokes Syndrome, Lancet, London, 1904, **1**, 1568.
- Laslett, E. E.: A Case of Digitalis Heart Block, Lancet, London, 1911, **1**, 19.
- Lea, C. E.: Recent Work on Heart Block, Practitioner, London, 1912, **89**, 655.
- Lea, C. E.: Dr. Thomas Spens: First Describer of Stokes-Adams Syndrome, Edinburgh Med. Jour., 1914, **13**, 51.
- Lea, E.: Complete Heart Block with Higher Ventricular than Auricular Rate, Lancet, London, 1915, **1**, 1289.
- Leitz, T. F.: Case of Adams-Stokes Disease, Maryland Med. Jour., September, 1907, p. 345.
- Lemann, I. J.: Study of a Case of Heart Block with Alternation of Systolic and Diastolic Jugular Waves, Jour. Am. Med. Assn., 1910, **55**, 1069.
- Levine, S. A.: Observations on Sino-Auricular Heart Block, THE ARCHIVES INT. MED., 1916, **17**, 153.
- Lewis, T.: Occurrence of Heart Block in Man and Its Causation, Brit. Med. Jour., 1908, **2**, 1798.
- Lewis, T.: The Effect of Vagal Stimulation on Atrioventricular Rhythm, Heart, 1914, **5**, 247.
- Lewis, White and Meakins: The Susceptible Region in A-V Conduction, Heart, 1914, **5**, 289.
- Lewis and Mathison: Auriculoventricular Heart Block as a Result of Asphyxia, Heart, 1910, **2**, 47.
- Lichtheim: Ueber einen Fall von Adams-Stokes'scher Krankheit mit Dissoziation von Vorhof-und-Kammerrhythmus, Deutsch. Arch. f. klin. Med., 1906, **85**, 360.
- Lichty, M. J.: Stokes-Adams Disease, Cleveland Med. Jour., August, 1910, p. 682.
- Lundsgaard, C.: Two Cases of Heart Block, Lancet, London, 1916, **1**, 125.
- Mackintosh and Falconer: Observations on Two Cases of Adams-Stokes Syndrome, Unassociated with Demonstrable Delay of Impulse Transmission, Heart, 1911, **2**, 222.
- Marin, K., Klinisch-experimentelle Beiträge zum totalen Herzblock, Mitt. a. d. med. Fagult. d. k. Univ. zu Tokyo, 1916, **15**, 125.
- Mathison, G. C.: The Cause of the Heart Block Occurring During Asphyxia, Heart, 1910, **2**, 54.
- Meakins, J.: Experimental Heart Block with Atrioventricular Rhythm, Heart, 1914, **5**, 281.
- Meyer, A. W.: Ueber Reizleitungsstörungen an menschlichen Herzen, Deutsch. Arch. f. klin. Med., 1911, **104**, 16.
- Michael and Beutten-Müller: Zur Klinik des Adams-Stokes'schen Symptomenkomplexes, Berl. klin. Wehnschr., 1907, **44**, 1474.
- Mollard, Dumas and Rebattu: Syndrome de Stokes-Adams sans lésion du faisceau de His, Arch. d. mal. d. cœur, 1911, **4**, 298.
- Mortenson, M. A.: Discussion of Heart Block, with Report of Case, Michigan State Med. Soc. Jour., 1914, **13**, 172.
- McCaskey, G. W.: An Ocular Method for the Diagnosis of Heart Block, Jour. Am. Med. Assn., 1907 **48**, 418.
- McDonald, J. A.: Heart Block, Indiana Med. Jour., July, 1907, p. 4.
- Nagayo, M.: Pathologisch-anatomische Beiträge zum Adams-Stokes'schen Symptomenkomplex, Ztschr. f. klin. Med., 1909, **67**, 495.
- Naish, A. E.: Premature Ventricular Beats in Heart Block, Quart. Jour. Med., 1913, **6**, 196.
- Naish, A. E.: The Ventricular Rate in Complete Heart Block, Brit. Med. Jour., 1913, **1**, 491.

Naish and Kennedy: Heart Block in Acute Rheumatic Carditis, *Lancet*, London, 1914, **2**, 1242.

Neuhof, S.: Complete Heart Block with Rapid Irregular Ventricular Activity, *Am. Jour. Med. Sc.*, 1913, **145**, 513.

Neuhof, S.: Functional Heart Block in Pneumonia, *Jour. Am. Med. Assn.*, 1914, **63**, 577.

Nomta, A.: Dissociation auriculo-ventriculaire complète chez une hérédosyphilitique deux grossesses successives sans incident, *Arch. d. mal. du cœur*, 1914, **7**, 305.

Northcote and Gossage: Partial Heart Block, *Brit. Med. Jour.*, 1906, **2**, 1217.

Oppenheimer, A., and Oppenheimer, B. S.: Three Cases of Adams-Stokes Syndrome with Histologic Findings, *THE ARCHIVES INT. MED.*, 1914, **13**, 957.

Parkinson, John: Auricular Filbrillation following Complete Heart Block in Diphtheria, *Heart*, 1915, **6**, 13.

Pardee, H. E. B.: Relation of Heart Block to Lesions of Auriculoventricular Bundle, with Report of Case, *THE ARCHIVES INT. MED.*, 1913, **11**, 641.

Peabody, F. W.: Heart Block with Infectious Diseases, *THE ARCHIVES INT. MED.*, 1910, **5**, 252.

Pearson, W.: Heart Block and Conduction of Cardiac Impulse, *Dublin Jour. Med. Sc.*, October, 1907, p. 256.

Pepper, W., and Austin, J. H.: Adams-Stokes Syndrome with Complete Heart Block and Practically Normal Bundle of His, *Am. Jour. Med. Sc.*, 1912, **143**, 716.

Peyton, T. H.: Stokes-Adams Syndrome, *Dublin Jour. Med. Sc.*, August, 1906, p. 109.

Pletnew, D.: Ein Fall von transversaler Dissoziation, *Ztschr. f. klin. Med.*, 1912, **74**, 10.

Porter, R. R. M.: Heart Block in Pneumonia, *Brit. Med. Jour.*, 1914, **1**, 858.

Price, T. W.: Auricular Fibrillation and Heart Block in Diphtheria, *Heart*, 1912, **3**, 233.

Purser and Davis: Case of Stokes-Adams Disease of Heart, *Australasian Med. Gazette*, 1911, **30**, 442.

Quinan, C.: The Adams-Stokes Symptom Complex with Report of a Case, *Am. Jour. Med. Sc.*, 1904, **127**, 403.

De Renzi, E.: Ueber die Stokes-Adams'sche Krankheit, *Berl. klin. Wchnschr.*, 1908, **45**, 861.

Robinson, A. A.: Adams-Stokes Syndrome, *Med. Rec. New York*, 1909, **75**, 970.

Robinson, G. C.: Case of Heart Block Illustrating Mode of Action of Vagus Nerve on Heart, *Missouri State Med. Assn. Jour.*, 1915, **12**, 363.

Routier, D.: Dissociation auriculoventriculaire transtoire dans le rhumatisme articulaire aigu, *Arch. d. mal. dur.coeur*, 1914, **7**, 316.

Rudolph, R. D.: Case of Heart Block in Jaundice, *Brit. Med. Jour.*, 1916, **1**, 522.

Rudlof and Loughhead: Case of Complete Heart Block, with Postmortem Findings, *Arch. Diagnosis*, 1914, **7**, 155.

Sakar, S.: Zur Kenntnis der Dissoziation des Herzens, *Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo*, 1915, **13**, 206.

Schabert, A.: Ueber klinischen Herzblock, *St. Petersberger med. Ztschr.*, 1913, **38**, 263.

Schmoll, E.: Adams-Stokes Disease, *Jour. Am. Med. Assn.*, 1906, **46**, 361.

Schmoll, E.: Zwei Falle von Adams-Stokes'scher Krankheit mit Dissoziation von Vorhof-und Kammer-Rhythmus und Lasion des His'schen Bundles, *Deutsch. Arch. f. klin. Med.*, 1906, **87**, 554.

Schreiber, E.: Ueber Herzblock beim Menschen. *Deutsch. Arch. f. klin. Med.*, 1907, **89**, 277.

Schwarzmann, J. S.: Ueber einen Fall von Herzblock mit paroxysmalem Vorhofflimern, *Zentralbl. f. inn. Med.*, 1914, **35**, 1001.

Senior, H. D.: Remarks on the Anatomy and Pathology of Heart Block. St. Louis Med. Rev., March, 1907, p. 241.

Souques and Routier: Trois cas de dissociation auriculoventriculaire d'origine neuro-musculaire, Arch. d. mal du coeur, 1913, **6**, 497.

Steiner, W. R.: Stokes-Adams Disease, with Report of Three Cases, Boston Med. and Surg. Jour., 1906, **155**, 135.

Stengel, A.: A Fatal Case of Stokes-Adams Disease with Autopsy, Showing Involvement of the Auriculoventricular Bundle of His, Am. Jour. Med. Sc., 1905, **130**, 1083.

Stengel and Pepper: Heart Block with an Indication of a General Hemisystole, Am. Jour. Med. Sc., 1910, **140**, 487.

Stoddard, C. H.: Stokes-Adams Disease, Wisconsin Med. Jour., May, 1905, p. 669.

Tait, John: The Action of Yohimbine on the Heart, with Special Reference to Toxic Heart Block, Quart. Jour. Exper. Physiol., 1910, **3**, 185.

Taussig, A. E.: Complete and Permanent Heart Block Following Use of Digitalis in Auricular Fibrillation, THE ARCHIVES INT. MED., 1912, **10**, 335.

Taylor, F.: A Clinical Lecture on Adams-Stokes Disease, Clin. Jour. 1911, **37**, 193.

Taylor, T. F. L.: Transient Heart Block Due to Intestinal Toxemia, Jour. Am. Med. Assn., 1908, **50**, 1246.

Thayer, W. S.: Adams-Stokes Syndrome, Persistent Bradycardia Involving Both Auricles and Ventricles. Remarkable Prolongation of As-Vs Interval, THE ARCHIVES INT. MED., 1916, **17**, 13.

Thayer and Peabody: Two Cases of Adams-Stokes Syndrome with Heart Block, THE ARCHIVES INT. MED., 1911, **7**, 289.

Tuley, H. E.: The Stokes-Adams Syndrome, Kentucky Med. Jour., 1912, **10**, 907.

Turrall and Gibson: Case of Adams-Stokes Disease Observed for More than Ten Years, Brit. Med. Jour., 1908, **2**, 1486.

Vaquez and Esmein: Maladie de Stokes-Adams pas lésion scléro-gommeuse du faisceau de His-Herzblock, Presse méd., 1907, **15**, 57.

Vickery, H. F.: Final Report on a Case of Adams-Stokes Disease, Boston Med. and Surg. Jour., 1908, **160**, 435.

Whipham, T. R.: Congenital Heart Block, Brit. Jour. Child. Dis., 1915, **12**, 321.

White, P. D.: Auricular Fibrillation and Complete Heart Block, Boston Med. and Surg. Jour., 1915, **173**, 431.

Wilkinson and Butterfield: Paroxysmal Heart Block, with Paroxysmal Auricular Fibrillation, Heart, 1915, **6**, 3.

Wilson, W. T., Jr.: Case of Complete Heart Block, Jour. Am. Med. Assn., 1915, **65**, 955.

Windle, J. D.: Heart Block from Drugs of the Digitalis Group. The Comparative Effects of Digitalis, Strophanthus, Squill and Apocynin, Heart, 1911, **3**, 1.

Windle, J. D.: Permanent Complete Heart Block: a Case with an Exceptionally Frequent Ventricular Rate, Heart, 1910, **2**, 102.

STUDIES IN THE VARIATIONS OF THE TONUS OF THE GASTRIC MUSCULATURE IN HEALTH AND DISEASE *

BURRILL B. CROHN,** M.D., AND ABRAHAM O. WILENSKY, M.D.
NEW YORK

The alterations in structure of any of the body organs, when produced by disease, are of greatest clinical importance when accompanied by disturbances in the function of the involved part. The function of the musculature of the stomach, that is, its motor function, is one of the most essential attributes of that organ; disturbances of this function characterize many of the earliest stages of gastric diseases. In this paper we have attempted to correlate the results of our studies on the variations of the functions of the gastric musculature in diseased conditions. Kymographic methods were utilized in their demonstration, as described by Cannon and Washburn¹ and by Carlson² and his associates, and studies of gastric hunger contractions and gastric tonus were carried on.

HISTORICAL

In 1877, von Pfungen³ demonstrated, in the antrum of the stomach of animals, contractions occurring regularly three times a minute.

Morat,⁴ in 1882, made use of a rubber balloon attached to the end of a stomach tube and recorded intragastric pressures. His tracings evidenced respiratory, cardiac and gastric elements.

In 1895, Moritz⁵ obtained readings of intragastric pressure under various conditions. He utilized the method of an inflated balloon attached to a stomach tube, which he introduced into the stomach. The normal pressure within the healthy stomach of man varied between 2 and 16 cm. of water. He demonstrated a difference in pressure between the antral and fundic portions of the stomach, and made some observations on himself after the administration of such drugs as

* Submitted for publication March 30, 1917.

* From the First and Second Medical Services, the Pathological Laboratory and the Gastro-Enterologic Department of the Dispensary of the Mount Sinai Hospital.

** This study was carried on under the tenure of a George Blumenthal, Jr., Fellowship in Pathology.

1. Cannon and Washburn: *Am. Jour. Physiol.*, 1911-1912, **29**, 441.

2. Carlson, A. J.: *Am. Jour. Physiol.*, 1912, **31**, 175 and 221; *ibid.*, 1913, **32**, 245.

3. Von Pfungen: *Centralbl. f. Physiol.*, 1877, p. 220.

4. Morat: *Arch. de Lyon méd.*, 1882, p. 882.

5. Moritz: *Ztschr. f. Biol.*, 1895, **24**, 313.

bicarbonate of soda and tartaric acid. He recognized, both in the fasting and in the digesting stomach, the occurrence of contractions which followed one another three to three and one-half times each minute, which contractions continued for periods of fifteen to ninety minutes, and which were separated by intervals of rest. The presence of food in the stomach inhibited these contractions. By means of double balloons he was able to demonstrate activity in the antrum, which was synchronous with a state of rest in the fundus.

Ducchessi⁶ applied the same method in animal experiments and found that an increase of intragastric pressure caused the appearance of rhythmic contractions. He showed distinct differences between contractions of the cardiac, fundic and pyloric parts of the stomach and confirmed in animals the presence of the rhythmic contractions described by Moritz in man. He was of the opinion that the empty stomach remained in a state of rest, but that the introduction of food or of the inflated balloon gave rise to the typical contractions which he observed. Excision of the celiac plexus was followed by a change in the contraction wave. With the occurrence of pathologic lesions a depression of gastric tone was observed.

Sick,⁷ in 1906, employed a complicated apparatus by means of which he was able to obtain records of intragastric pressures and stomach contractions, and specimens of stomach contents for chemical examination. Using the facts obtained from normal subjects as criteria, he made observations also in pathologic conditions.

Boldyreff,⁸ in exhaustive studies on the alimentary canal, demonstrated waves of contraction originating in the stomach and sweeping downward throughout the entire extent of the alimentary canal. They bore some relation to the empty state of the stomach, disappearing with the ingestion of food and reappearing some time later.

In 1911, Cannon and Washburn,¹ in the course of investigations on the cause of hunger, demonstrated periods of gastric excitability evidenced by peristaltic waves, which occurred synchronously with sensations of hunger. The conditions necessary for the appearance of these contractions were a tonic state of the neuromusculature, plus some increase in the intragastric pressure. The point of origin of these contractions was not fixed. Most important of all, Cannon and Washburn¹ maintained that hunger contractions were evidences of healthy tone in a normal stomach.

About a year later, Carlson² was fortunate in finding a man with a gastric fistula which allowed of physiologic investigations. In this man

6. Ducchessi: *Arch. ital. de biol.*, 1897, **27**, 61.

7. Sick: *Arch. f. klin. Med.*, 1906-1907, **88**, 169.

8. Boldyreff: *Zentralbl. f. Physiol.*, 1904, **18**, 489.

he was able to confirm all the statements of Cannon and Washburn.¹ He demonstrated in the kymographic tracings two types of contraction: one, a slow, periodic wave due to the normal tonal variations, which passed over the stomach three to four times a minute; second, a type of more powerful contractions, occurring in groups, lasting from fifteen

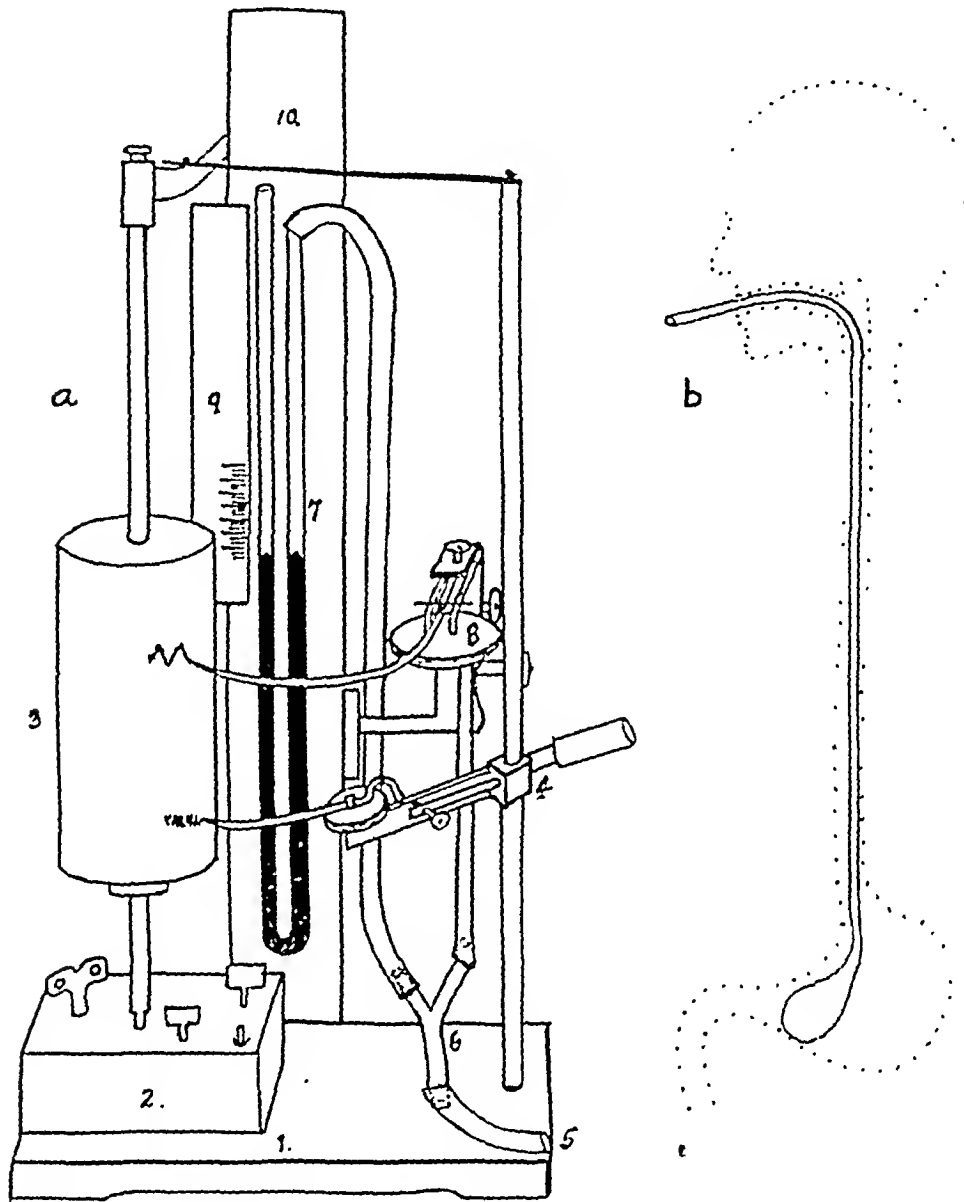


Fig. 1.—*a*, 1. Stand. 2. Clock work for revolving kymograph. 3. Kymographic drum. 4. Bracket supporting tambour and needle and connected with pneumograph about patient. 5. Tube connecting with balloon in patient's stomach and connecting with Y tube (6) to manometer (7) and tambour and needle (8). 9. Manometer scale. 10. Upright fixed to stand supporting apparatus, *b*, balloon and tube in stomach (diagrammatic).

to sixty or more minutes and separated by long periods of comparative inactivity. These last corresponded to the sensations of hunger and were easily inhibited by various causes, such as the act of swallowing or

the administration of various foods and drugs. The period of contractile activity was always accompanied by a period of slow gastric secretion.

We were enabled to apply this physiologic method in a series of pathologic cases in the hospital.⁹ These cases included practically all the varieties of gastric diseases ordinarily encountered, such as gastric neuroses, gastric atony, vagotonia, secretory disturbances and organic lesions such as ulcer and carcinoma.

METHOD

A uniform technic was followed in all of these cases; an apparatus was used practically identical with that employed by Cannon and Washburn¹ and by Carlson.² The patient swallowed a collapsed toy balloon attached to the end of a narrow-caliber rubber tube. The free or proximal end of the latter was attached by a Y tube to both a mercury manometer and a tambour with its recording needle; the movements of the needle were in turn recorded on a slowly revolving drum. The respiratory element of the curve was controlled

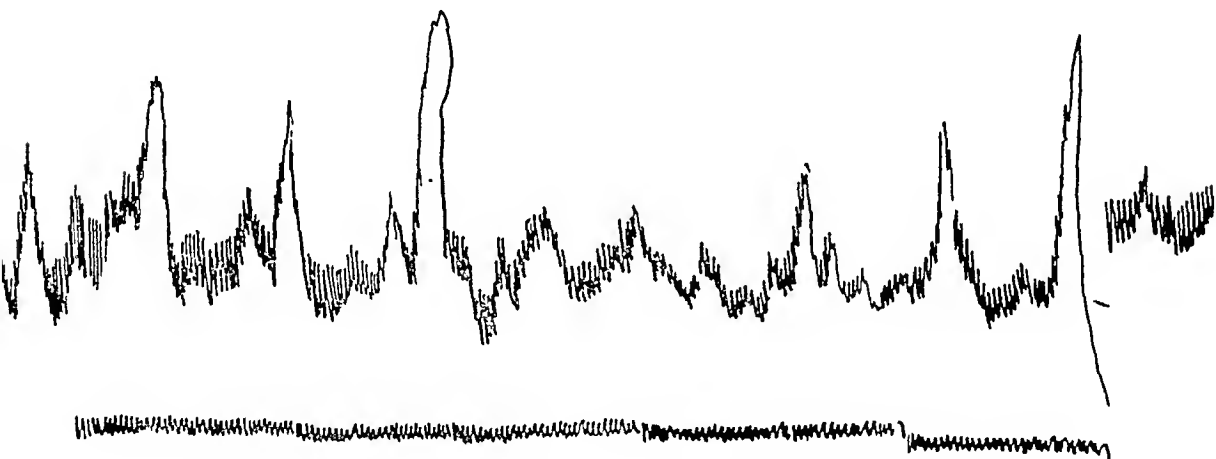


Fig. 2.—Kymograph tracings taken from normal individuals showing normal tonus and hunger contractions.

In this and the following figures the upper curve represents the gastric variations, the lower curve is a control obtained from a pneumograph fastened about the lower thorax and upper abdomen.

by a pneumograph fastened over the lower thorax and upper abdomen. Time was recorded manually in minutes. Observations were maintained for periods of from one-half hour to one hour and in cases where no contractions were observed in this time, the observation was repeated on a subsequent day. Extraneous influences, such as the presence of food, swallowed saliva, or other physical disturbances, were eliminated. In practically all instances the patients reposed quietly on the table, and frequently dropped off to sleep during the course of the observation. No record was accepted when the patient evidenced intolerance of the tube and balloon.

9. We acknowledge our indebtedness to Drs. Brill, Libman, Manges and Meyer of the first and second medical services of the Mount Sinai Hospital, and to Dr. Aronson, chief of the gastro-enterologic department of the dispensary, for their courtesy in permitting us to make these observations on the patients under their care.

OBSERVATIONS

Gastric Neuroses.—These include those customarily seen in hospital ward or dispensary service. The records obtained from these patients did not vary particularly from those obtained from normal persons. That is, they evidenced normal tonal waves, recurring rhythmically and usually regularly, sometimes as slowly as once per minute, usually more rapidly, as two or three times per minute. The average tonal rise corresponded to about 5 mm. Hg. In the cases of neurosis the regular rhythm was sometimes disturbed by a varying degree of irregularity. The hunger contractions, which were always present in these organically sound stomachs, appeared singly or in groups. They were characterized by a steady rise of the lever, lasting over two or three respirations, until a pressure of 20 to 30 mm. Hg was registered, and following which there was a sudden drop to the base line. The rise of the lever

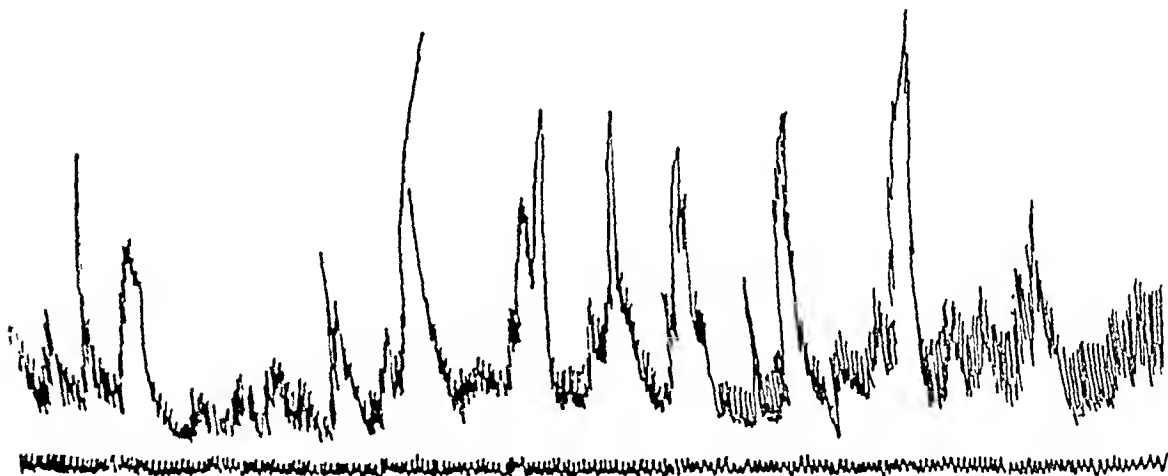


Fig. 3.—Tracing from a case of gastric neurosis, demonstrating good tone and continuous hunger contractions.

may be continuous, corresponding to a single powerful contraction, or may consist of several superimposed contractions. The fastigium is held for a fraction of a minute only. Occasionally, on the introduction of the balloon, no contractions appeared at first, but after a lapse of ten to twenty minutes the inhibitory influence of the foreign body passed away and tonal waves and hunger contractions made their appearance.

Vagotonia.—In a well marked case of vagotonia, hunger contractions predominated in the curve and demonstrated an extreme degree of excitability, the contractions following one another in rapid succession and without pause for comparatively long periods of time.

Functional Secretory Cases.—These include hyperacidities, subacidities and anacidities. These regularly show no disturbance in the motor function. Occasionally in marked instances of continuous hyper-

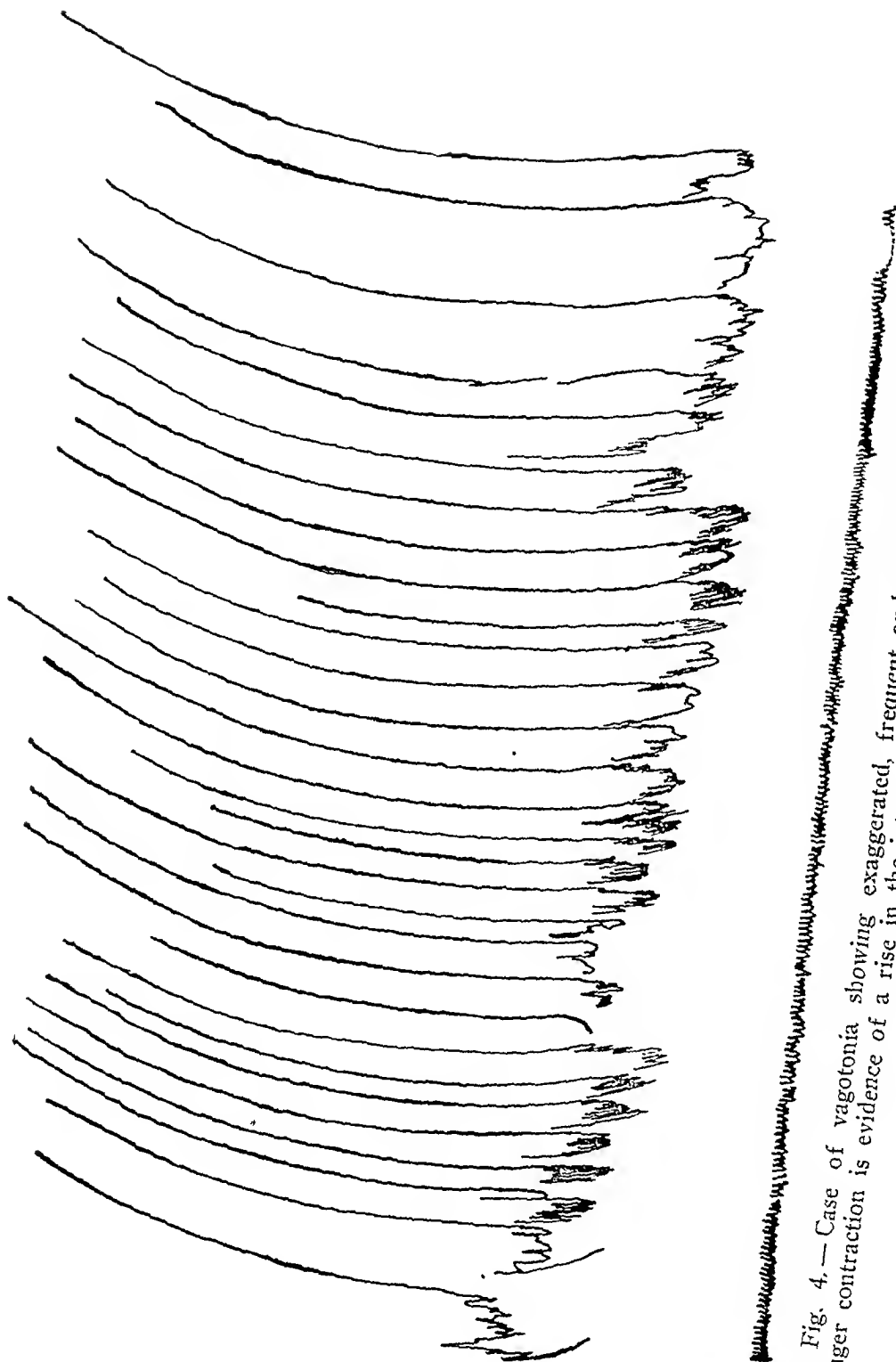


Fig. 4. — Case of vagotonia showing exaggerated, frequent and continuous hunger contractions; each hunger contraction is evidence of a rise in the intragastric pressure of 30 to 40 mm. Hg.

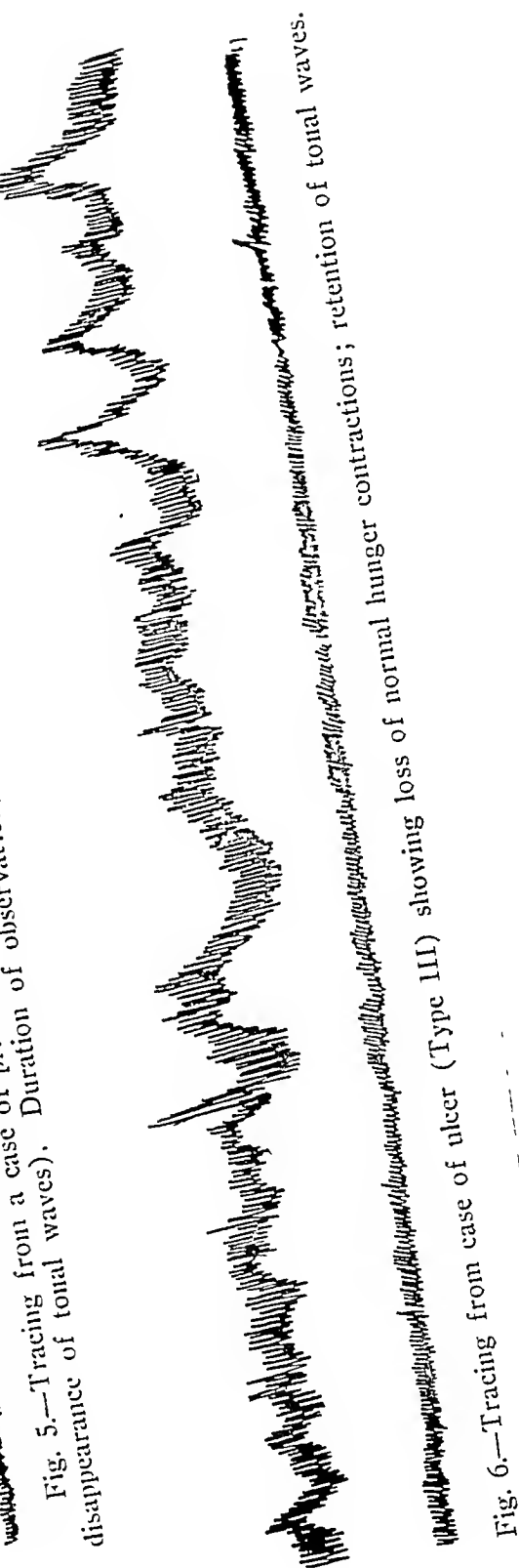
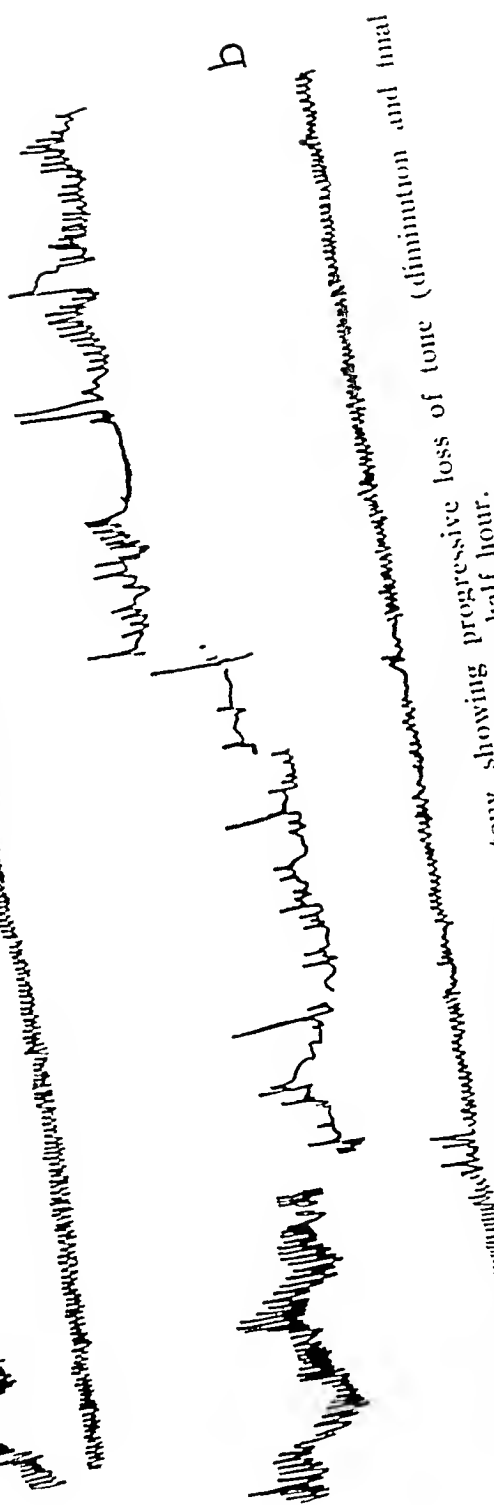


Fig. 5.—Tracing from a case of primary atony, showing progressive loss of tone (diminution and final disappearance of tonal waves).

Fig. 6.—Tracing from case of ulcer (Type III) showing loss of normal hunger contractions; retention of tonal waves.

secretion, the constant presence of acid secretion in the fasting stomach inhibits the contractions, an appearance of atony being given.

Primary Atony.—This is evidenced by a diminution or disappearance of tonal contractions and a disappearance of hunger contractions. At the beginning of the observation moderate tonal contractions may appear, but these soon disappear and leave a curve which is characterized by absence of elevations and the maintenance of a continuous and unchanging level.

In cases of incompletely developed atony one occasionally may see small contractions or groups of moderate tonal waves, but the general curve as observed for the entire period is usually devoid of such demonstrations of tonus on the part of the gastric musculature.

Secondary atony accompanying organic lesions will be discussed under the appropriate headings.

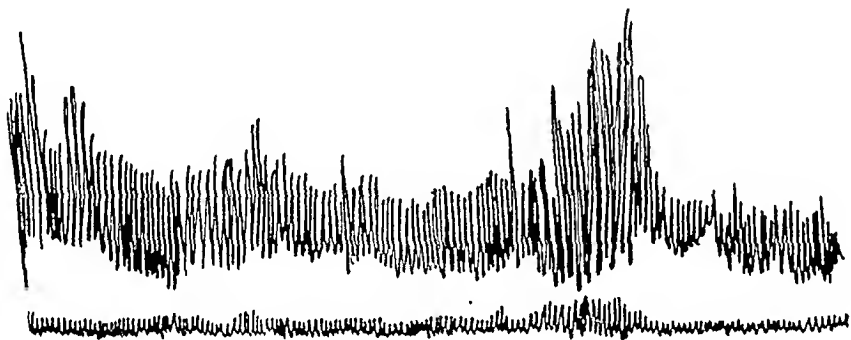


Fig. 7.—Atony secondary to callous ulcer on lesser curvature. Note complete absence of tonus and hunger waves.

We have not had an opportunity to study cases of pure gastritis. Catarrhal inflammations frequently complicate other anatomic lesions such as ulcer or carcinoma, and the descriptions of these conditions necessarily would include the effect of the catarrhal condition plus that of the main lesion. A case, however, has been reported in the literature¹⁰ in which a gastritis was accompanied by a practically complete absence of motor activity.

*Gastric and Duodenal Ulcer.*¹¹—No differentiating characteristics between these two types of ulcer could be demonstrated. It is of advantage to describe under different headings the tracings obtained.

1. Ulcer cases with practically normal tracings. These represent about one-fifth of the tracings.

2. Cases with retained tonal contractions, but irregular and isolated hunger contractions. These, too, represent about one-fifth of the cases.

10. Hamburger and Luckhardt: Jour. Am. Med. Assn., 1916, 66, 1831.

11. This subject is described in detail by one of us in another article to be printed in the Annals of Surgery.

3. Ulcer cases, characterized by the disappearance of hunger contractions, but with retained tonus. These comprise also about one-fifth of the cases. Groups 2 and 3 together may be classed as those giving irregular tracings.

4. Cases of secondary atony. These are fewer in number. All gradations of this disturbance can be demonstrated. The presence of large, deeply punched out lesions in the body of the stomach has an inhibiting effect on the motor activity, and atonic conditions result. Pylorospasm is frequently associated with these large ulcers.

5. Cases of pyloric stenosis. In the early stages there is increased tonus and more prolonged and sustained hunger contractions. In the late stages a fatigue atony may appear. Between these two limits, all stages are observed.

Carcinoma Cases.—Here, too, the motility of the stomach may exhibit all changes from hyperactive conditions to marked degrees of atony. When the tumor is comparatively small, or when it is still limited to the superficial layers of the stomach wall, no disturbance is noticeable in the muscular activity. The tonus and hunger contractions are of normal volume and repeat themselves with the regularity customary to healthy stomachs. This is also true in the case of those tumors in the body of the stomach which may or may not be large in extent, but which are limited practically to the mucous membrane.

Tumors near the pyloric sphincter may be differentiated in accordance with the production or absence of a stenosis. In those cases with malignant stenosis, the same facts were observed as with the benign stenosis.

Carcinomata of the stomach are usually accompanied by various degrees of chronic gastritis, and in many cases the latter assumes a dominant position in regard to the disturbances of function and causes a practical disappearance of all muscular activity.

Tabes with Gastric Crises.—One such case has been studied, the observation being made during the intervals between attacks. The curve is one of complete incoordination, periods of marked overactivity following periods of atony with an absence of the normal rhythm. All of these phases were visible during a comparatively short period of observation.

DISCUSSION

The smooth muscle wall of the stomach is arranged in three layers and accomplishes a predominating churning motion in the fundus of the stomach and a predominating propulsive exertion in the antrum. In addition, there is provided a valve at both the entrance to, and the exit from, the stomach. Inasmuch as the natural tonicity of smooth

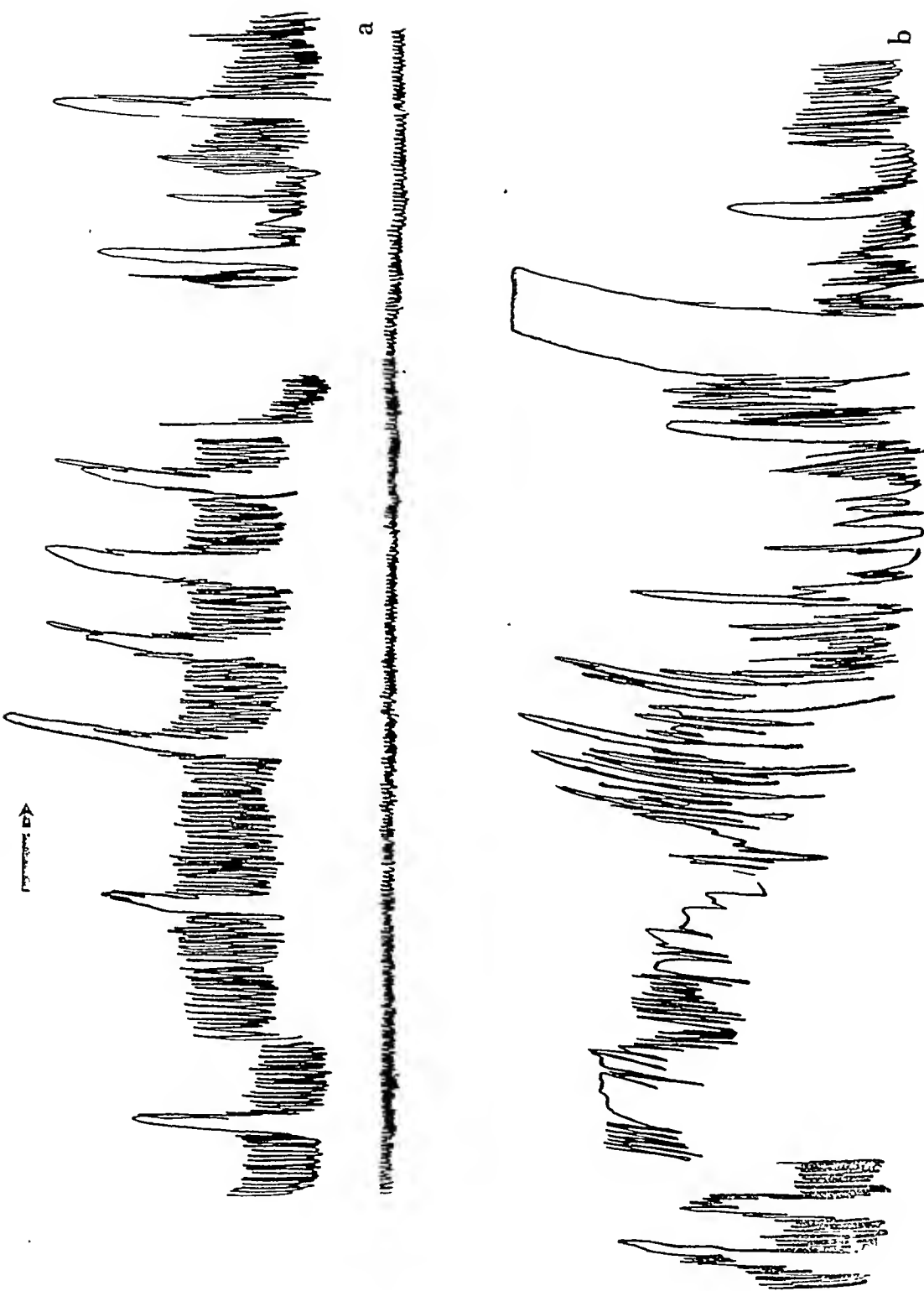


Fig. 8.—Benign pyloric stenosis. The hunger contractions are broader, more sustained and frequent. The middle tracing is the control.

muscle fiber is always in evidence, it follows that the entire structure is constantly in a state of contraction on its contents. The presence of valve formations at both ends of the stomach establishes conditions for intragastric pressures which would naturally vary with the activity of the organ.

This variation in the natural tension of the muscle fiber produces what has been called by Cannon and Carlson the "tonus contractions" of the stomach. In a healthy organ these tonal variations are repeated regularly and rhythmically three to four times each minute, and establish an intragastric pressure of an average moderate degree.

It has been conclusively shown in purely physiologic work that the appearance of any active contraction of the stomach is dependent on a normal tonus of the musculature, and has its origin in an increase in the intragastric pressure.

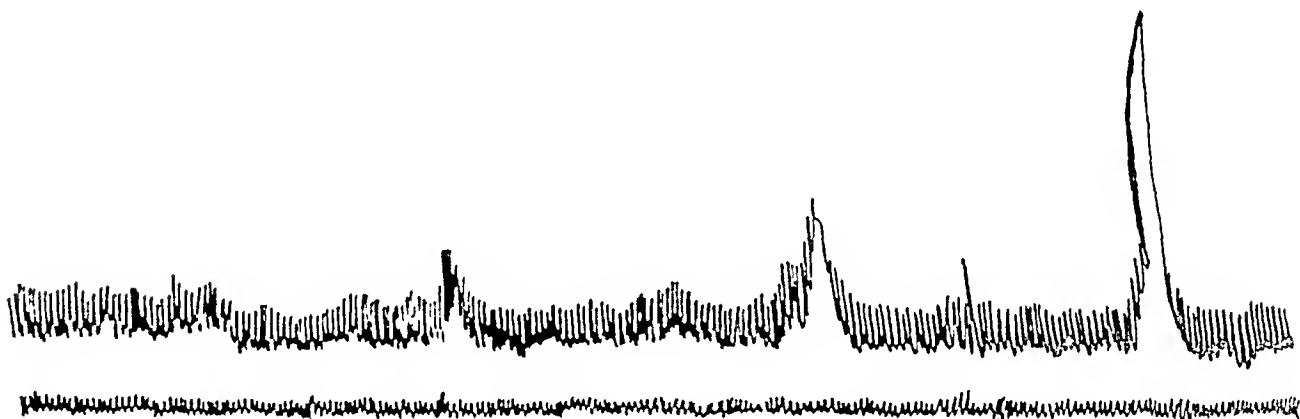


Fig. 9.—Same case as illustrated in Figure 8, taken six months later. Note that the tracing is now one of secondary atony, such as accompanies ectasia.

Tonus Contractions.—The tonus contractions which the kymographic drum records originate in the gastric musculature. Both Ducchessi and, more recently, Alvarez^{11a} demonstrated like contractions of a spontaneous nature in excised portions of the stomach wall, the three portions of the viscus (cardia, fundus and antrum) each exhibiting a characteristic type of movement. With our technic, the introduction and inflation of the balloon, by raising intragastric pressure, gives rise to these typical tonus contractions, as explained by Cannon. That the contractions can arise either from the fundus or the antral portions, was clearly proved by Sick, who obtained contractions from both ends in the same person, the fundus contractions being weaker and of less amplitude than the antral. It is probable, however, that in the cases examined by us, the balloon, which, even when inflated, is only the size of a medium large lemon, moves easily in the stomach.

11a. Alvarez, W. C.: Jour. Am. Med. Assn., 1915, **65**, 388; *ibid.*, Am. Jour. Physiol., 1916, **41**, 321; 1916, **40**, 358; 1917, **42**, 422.

and is soon pushed down by the contractions to the antral region, where the larger hunger contractions are produced. Rogers and Hardt,¹² by enclosing a smaller balloon filled with bismuth within a larger inflatable balloon, demonstrated vigorous contractions at the fundus, sweeping down over the antrum. Alvarez¹³ found the cardia and lesser curvature to be the most irritable portion of the stomach. Keith¹⁴ suggested the presence of a rate-making node on the lesser curvature near the cardia.

The tonus contractions appear in all stomachs approaching the normal or acting in an efficient physiologic manner. They are diminished or absent in the following conditions:

Gastric Atony.—This refers to the simple atony often seen as part of the picture of a gastric neurosis, or to the atony secondary to pulmonary tuberculosis, secretory disturbances of the stomach, etc. The atony here may appear only after the lapse of ten to fifteen minutes of observation, or after the primary contractions incident to the introduction of a foreign body have subsided. In such an instance the atony is progressive. In tonic stomachs there may be inhibition at first, but soon the tonus contractions appear and are thereafter steadily maintained throughout the observation. In a tonic stomach the amplitude and rate of contraction are usually constant; in cases with disturbed tone, the contractions are irregular, unequal, and the rate often variable.

Atony Secondary to Operation on the Stomach.—This subject has been more fully described in a recent paper by the authors.¹⁵ Suffice it to say that a pre-operative state of atony may continue after operation, particularly after gastro-enterostomy. The conclusions of the former paper were noted many years ago by Ducchessi¹⁶ and Denechau.¹⁷

The recovery of tone in the cases benefited by operation is progressive and is strikingly illustrated by our curves.

Ectatic Atony, or Atony Secondary to Pyloric Obstruction.—Such an atony appears as a late stage of mechanical pyloric obstruction, or is secondary to the pylorospasm of ulcer, distant from the pylorus. It is of marked degree and is the most complete of any observed.

Increased tonus is observed less frequently than diminished tonus; it is seen in irritative conditions of the vagus, as part of the picture in

12. Rogers and Hardt: Am. Jour. Physiol., 1915, **38**, 274.

13. Alvarez, W. C.: Am. Jour. Physiol., 1916, **40**, 585.

14. Keith: Quoted from Alvarez; see Footnote 13.

15. Wilensky and Crohn: Am. Jour. Med. Sc., 1917, to be published.

16. After grave lesions the curve of tonicity remains constantly depressed and the wave of contraction is distinctly periodic. ("Après des graves lésions, la ligne de tonicité se maintient constamment très déprimé et la fonction motrice est nettement périodique." Arch. ital de biol., 1897, **27**, 61.)

17. Denechau: Paris Thesis, 1907.

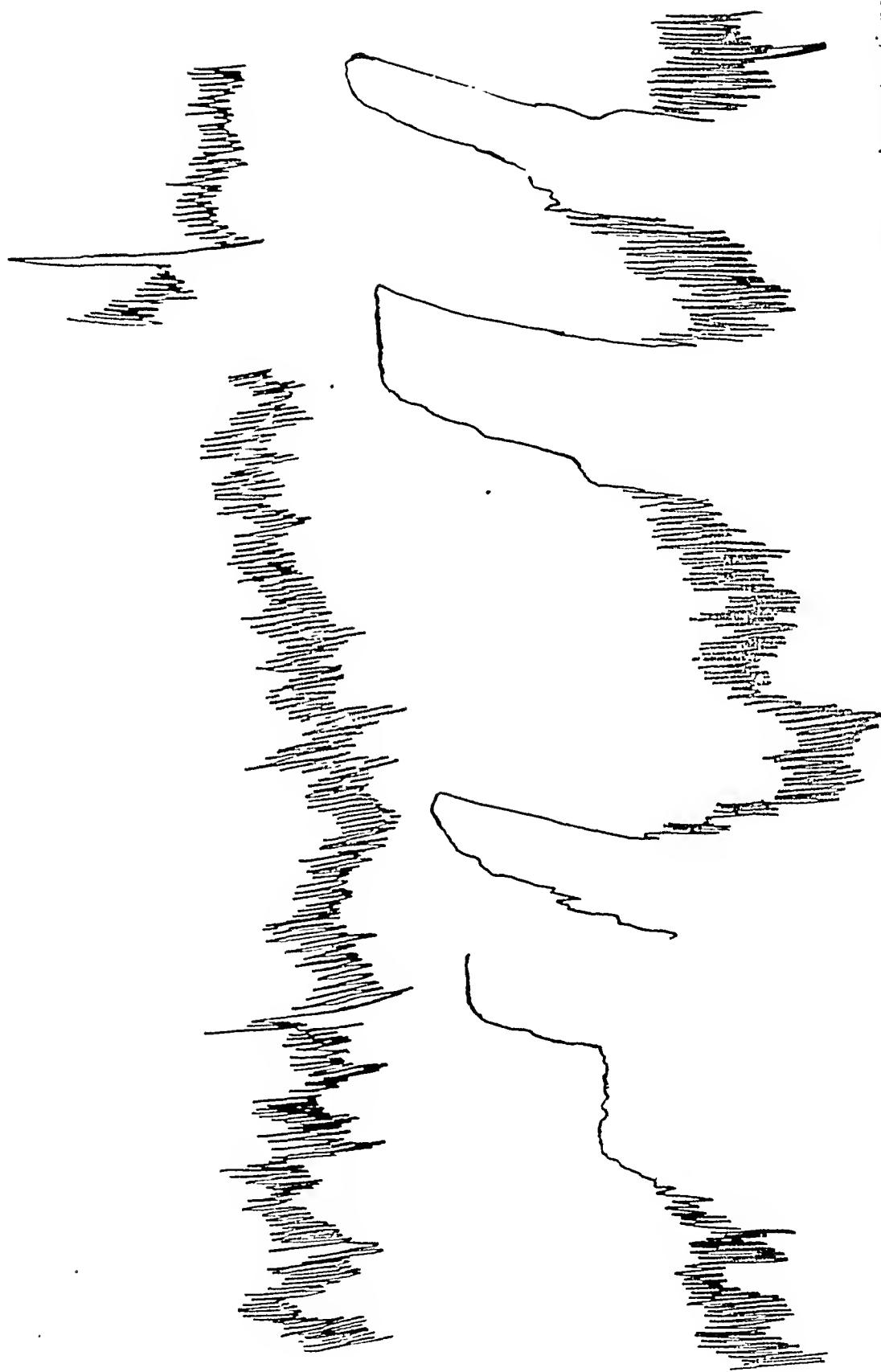


Fig. 10.—Malignant pyloric obstruction. Many of the hunger contractions are sustained and represent tetanic contractions of the empty viscus. (Control curve not given.)

tabes with gastric crises, and in the early stages of mechanical pyloric obstruction. In a case of carcinoma ventriculi, with infiltration of the mucosa with neoplastic tissue, increased tonus was observed, though no pyloric involvement occurred. This was due to rigidity of the wall of the viscus as well as to actual diminution of the interior space of the organ, the stomach assuming the appearance radiographically typical of a "leather-bottle" stomach.

Hunger Contractions.—In discussing the appearance of hunger contractions on our kymographic records, while we must agree with both Cannon and Carlson that hunger contractions are evidence of normality in the stomach, yet exceptions do occur, for we have observed the maintenance of good hunger contractions in cases in which gastric or duodenal ulcer was demonstrated at operation. Exceptions occur, however, in a small number of instances; as a rule, patients from whom a tracing has been obtained in which good and frequent hunger contractions occur, have proved at exploratory operation to be devoid of an organic lesion.¹⁸

The hunger contractions do not usually appear for the first few minutes of the observation, but once established, they follow each other in regular rhythm, separated by an interval which varies in each person, being in some ten to fifteen seconds; in others as long as sixty seconds apart. Sporadic or isolated contractions are less significant. The height of the contraction also varies, depending on the tonicity of the organ, being from 10 to 30 or 40 mm. Hg. Contractions of the nature of hunger contractions, of less than 10 mm. Hg. are really to be regarded as slightly exaggerated tonus waves, and represent the transition between tonus and hunger contractions.

Absence of hunger contractions is noted in atony, primary or secondary, and in organic lesions of the stomach and duodenum, particularly in ulcer. Carlson¹⁹ observed diminution of tonic contractions in dogs in which the vagi had been severed.

Exaggeration of hunger contractions has been noted in conditions of vagus excitation. May²⁰ noted contractions three times the normal height on stimulating the vagus.

In pyloric stenosis we have noted that the nature of the contraction may be changed so that the summit of the contraction curve instead of being sharp or acuminate, with the fall of pressure sudden and immediately following the fastigium, is rounded or sustained as a plateau. Such a sustained elevation may endure for one, two or three minutes and represents a tonic spasm or tetany of the gastric musculature. It

18. Wilensky and Crohn: Tr. Am. Gastro-Enterol. Assn., 1916.

19. Carlson, A. J.: Am. Jour. Physiol., 1913 32.

20. May: Jour. Physiol., 1904. 31, 260.

is pathognomonic, and was observed in two cases in which visible abdominal peristalsis was also evident. A similar condition was observed by Sick⁷ and by Carlson and Ginsburg²¹ in children with mechanical obstruction at the outlet of the viscus.

The case of tabes with gastric crises represents all phases of tonus from atony to hypertonicity, but is characterized by a complete absence of uniformity and by the occurrence of constant and unsystematized variations. The stomach seems to be in the same condition of ataxia as are the extremities, the bladder and the rectum.

A comparison between our interpretation of the kymographic tracings and the results of the Roentgen-ray examinations shows a fair degree of similarity. The most striking point is that good tonus con-

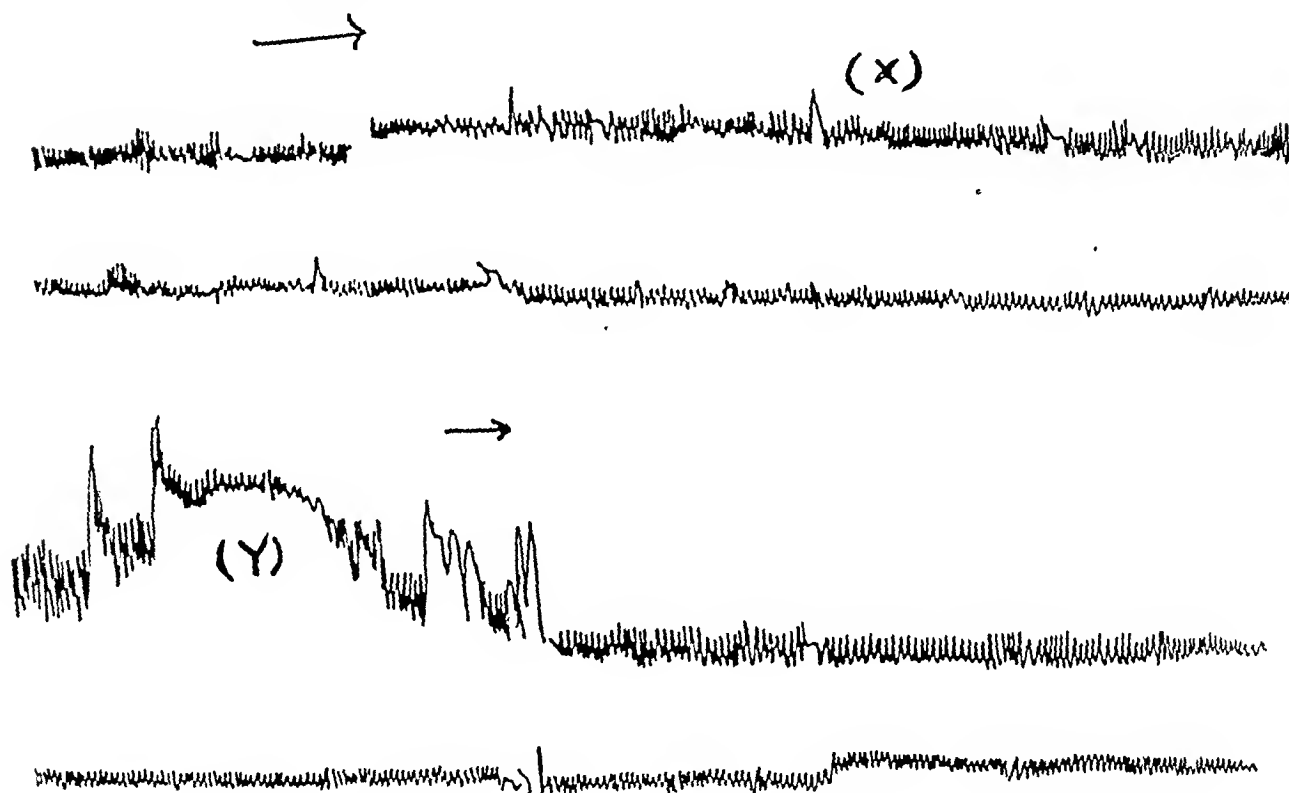


Fig. 11.—Tracing from a case of tabes with gastric crises. All phases are seen, from complete atony in the first few minutes to hyperatony, and even a sustained tetanic contraction as observed at (Y). The latter is often immediately followed by a long period of atony. Duration of observation, one-half hour.

tractions on the tracings signify good motility and normal emptying time of the stomach. No relationship exists between the tonus and hunger contractions demonstrated in the kymographic tracings, and the digestive peristalsis seen under the fluoroscope. As a rule, the tone of the stomach in the fasting state gives no indication of the degree of activity during digestion, and a state of atony in the fasting stomach

21. Carlson and Ginsburg: *Am. Jour. Physiol.*, 1915, **39**, 310.

may, under the stimulus of active digestion (barium-zoolak mixture), give place to fair, or active, or even hyperactive peristalsis. On the other hand, a complete absence of tonus contractions in one of the cases studies, corresponded with a complete absence of digestive peristalsis as seen under the fluoroscopic screen.

It has become evident from the data which we have collected to date, that hunger contractions and digestive peristaltic contractions are not identical. In fact, in Boldyreff's⁸ experimental studies on dogs, a disappearance of hunger contractions after the introduction of food into the stomach was clearly demonstrated.

SUMMARY

We may summarize our findings under the following captions:

1. The human fasting stomach, into which has been introduced an inflated balloon connected at its distal end with a registering tambour, gives, normally, evidence of periodic variations of tone, at the usual rate of three to four waves per minute. Hunger contractions of greater amplitude, and caused by more rapid increases in intragastric pressure, occur singly or in groups.

2. The appearance of these two types of waves characterizes a normal stomach.

3. No disturbance was noted in purely secretory or other functional gastric disturbances.

4. The occurrence of atony of the stomach, both primary and secondary, is marked by the disappearance of hunger contractions, and when advanced, also of the tonal waves.

5. Organic disease of the stomach, including ulcer and carcinoma, disturbs the motor function of the stomach, frequently causing a disappearance of the normally existing hunger contractions. In gastric or duodenal ulcer the normal tonal variations may be maintained, but usually are disturbed, one or both elements disappearing.

6. In pyloric stenosis, either benign or malignant, the tonus is at first markedly increased, the occurrence of gastric tetanic contractions often being observed. As the stenosis progresses, the features of secondary atony of the gastric musculature may supervene.

7. Tabes, with gastric crises, gives evidence of complete incoordination of the neuromuscular control of the organ.

8. There is little or no correspondence between the tonal and the hunger contractions of the fasting stomach and the digestive peristalsis of the viscus after a meal.

9. The method utilized in these experiments is a physiologic one, well adapted to a study of the variations in the functional capacity of the gastric musculature in health and disease. It is not, primarily, a means for diagnosis.

AN ERROR IN THE ELECTROCARDIOGRAM ARISING IN THE APPLICATION OF THE ELECTRODES *

HAROLD E. B. PARDEE, M.D.

NEW YORK

In the course of work with the electrocardiograph, there has come to my attention a phenomenon which introduces an error so large as to be of considerable importance. It is evident in Figure 1, and consists in the fact that when a constant difference of potential is applied at two points of the circuit containing the galvanometer and the patient, the resulting deflection of the string takes the form of a quick jump, as quick as the instrument can make, followed by a slow partial return toward the base line. The return takes the form of a curve such as can be seen in the figure (Fig. 1), and has a duration of from 0.1 to 0.4 second in different instances, being short when the overshoot is small, longer when it is large. When the string reaches this new level the deflection remains constant, the movements due to the heart's currents being superposed on this new base line as they were on the former one. The overshooting and slow return are usually evident to the eye of the observer in the process of standardization which is carried out before taking each lead of the electrocardiogram.

That others encounter this phenomenon is certain, for I have seen it in the records of two operators, and just recently Robinson¹ has described what must be this overshooting when he says, "Only those records have been used in which this adjustment (standardization) did not render the string sufficiently slack to cause any marked fling, which results in a definite deformity of the curves." Slacking the string is necessary when standardizing for a high resistance, but slacking the string does not lead to the appearance of "fling"; on the contrary, it causes the deflection to become slower, and to reach its maximum more gradually. A *tight* string may become periodic and go too far at first, but never when working at the sensitiveness used for electrocardiograms, unless the field strength of the magnet is very weak.

* Submitted for publication Feb. 5, 1917.

* From the Department of Physiology, College of Physicians and Surgeons, Columbia University, and from the medical services of the New York Hospital.

1. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, *THE ARCHIVES INT. MED.*, 1916, **18**, 830.

As it is customary to standardize so that a difference of potential of 1 millivolt placed in series with the galvanometer and the patient will produce a constant deflection of 1 cm. in the base line of the record, it is readily seen that the above condition produces an error in the height of the waves of the electrocardiogram. The differences of potential producing the Q, R and S waves being of practically instantaneous production, will cause the instrument to overshoot, as it does when we apply the standard current to a degree proportional to the magnitude of the currents of the Q, R and S waves. The P and T waves, being of more gradual onset, will allow, during their development, a varying degree of the gradual return toward the base line so evident in the figure, and will accordingly not be increased proportionally to their height — will not be so high as the quicker waves — for the same strength of current within the heart. The net result then

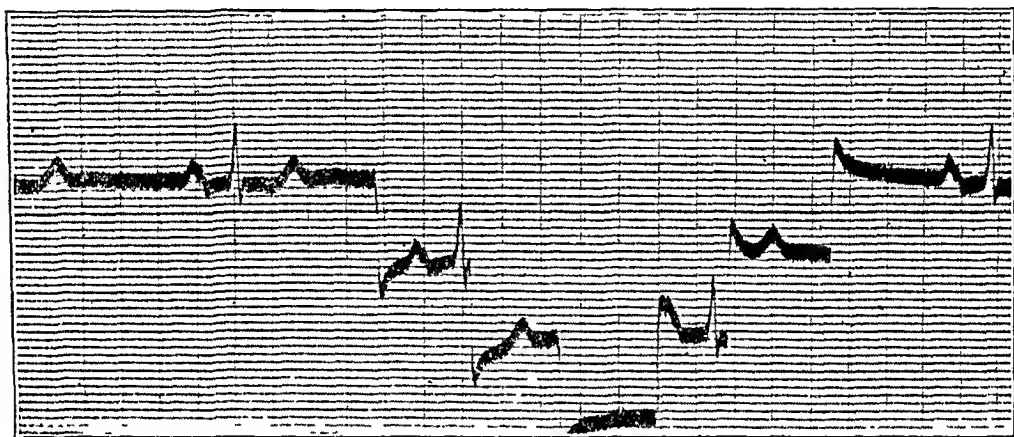


Fig. 1.—Application of successive millivolts in series with galvanometer and patient. German silver electrodes, Lead II; resistance measured as described, 5,000 ohms.

In this and all succeeding records the time interval between the corresponding line of successive pairs of ordinates is equal to 0.20 second. The distance between abscissae, 1 mm. in the originals, represents 0.1 millivolt.

All records should be read from left to right.

is a deformation of the electrocardiogram, and as this condition may be operative to a different extent in each lead, varying, as we shall see, with the apparent resistance, it will make impossible the comparison of records from the same person taken at different times, and will preclude the possibility of working out the direction of the potential within the heart which gives rise to a given wave or peak in the three leads.²

It was found that this effect was obtained only in cases in which

2. Einthoven, Fahr and de Waart: Ueber die Richtung u. die manifeste Grösse, etc., *Arch. f. d. ges. Physiol.*, 1913, **150**, 275. Also Pardee, H. E. B.: Form of Electrocardiogram, *Jour. Am. Med. Assn.*, 1914, **62**, 1311.

the resistance through the patient was relatively high, over 2,000 or 2,500 ohms. It appeared best when the resistance reached 4,000 ohms or more, being increasingly evident with higher resistance. Resistance through the patient was measured by substituting in the galvanometer circuit a resistance box instead of the patient, and determining the number of ohms which must be used in this box in order to make the deflection of the string equal to the deflection caused by the same potential

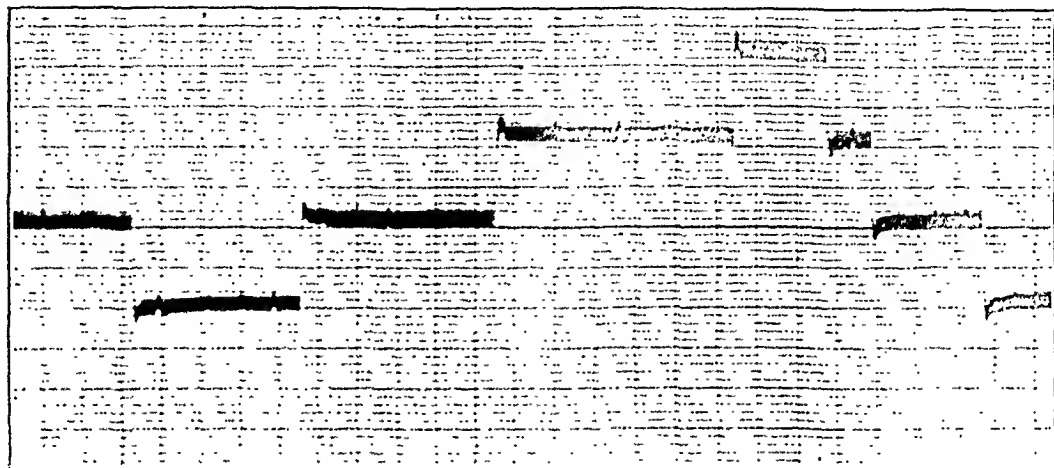


Fig. 2.—Application of successive millivolts as before, except that the lead is from the two legs, in order to minimize the electrocardiogram and make the overshooting more plainly visible; resistance 3,500 ohms.

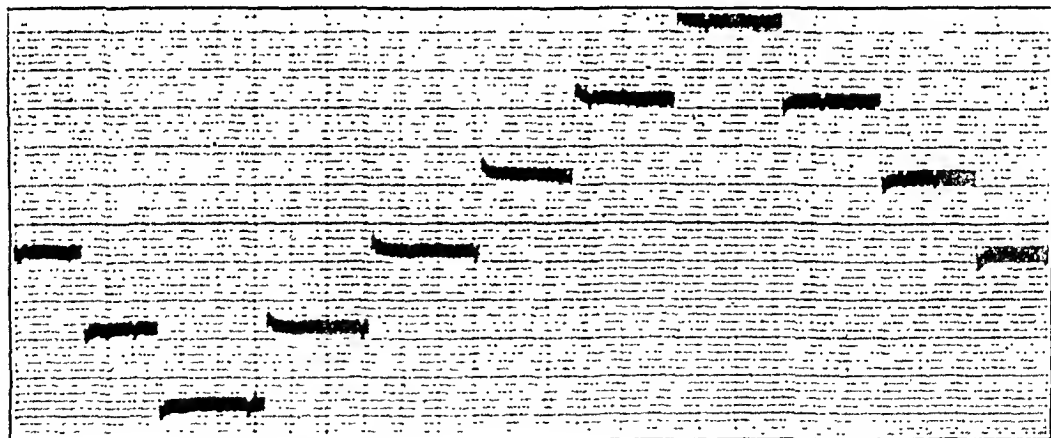


Fig. 3.—Conditions the same as in Figure 2, except that nonpolarizable electrodes were used as described in the text; resistance 3,600 ohms.

when introduced in the circuit of the patient and galvanometer; that is, 1 cm. deflection for 1 millivolt in each case. As a rule, the resistances measured by this method vary from about 500 to 1,500 ohms, usually about 1,000 ohms.

It was thought at first that this overshooting effect might be due to polarization of the electrodes, since these were not of the conventional nonpolarizable type. They consisted of a plate of German silver

about 12 by 25 cm. This was placed on the forearm or leg after the skin had been covered by a bandage soaked with strong salt solution, and the bandage was then continued over the outer surface of the metal plate. The plate was connected to the wires going to the galvanometer.³ Polarization of the electrodes as a cause of the phenomenon was disproved by two observations: (1) The outer layer of bandages was removed from the outer surface of the metal plate and the plate was removed. The bandage being left about the extremity, its free end was immersed in a porous cup of salt solution, and this was set in a solution of zinc sulphate. The wires were attached to an amalgamated zinc plate immersed in this solution. This is a true nonpolarizable cell, and a record of the patient under these conditions showed the same resistance and the same overshooting on the application of a millivolt

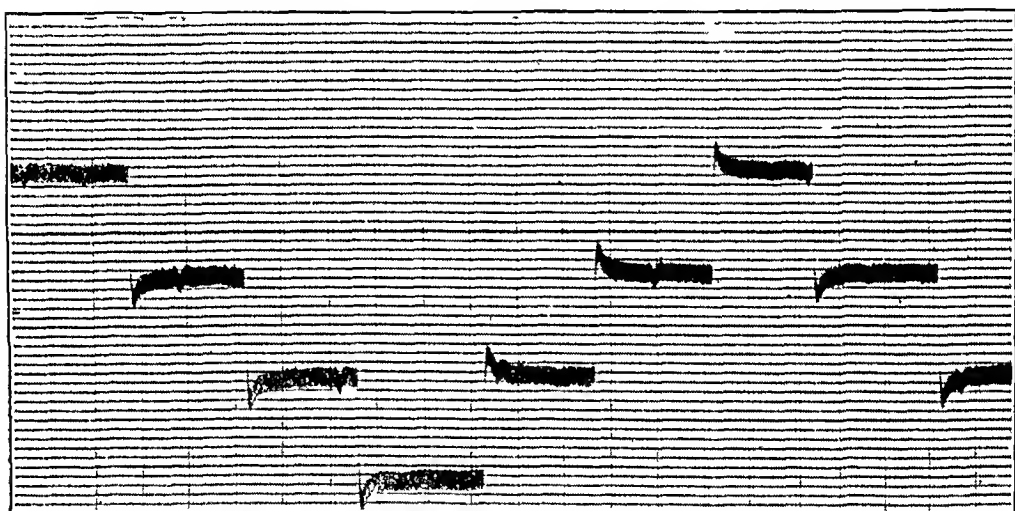


Fig. 4.—Application of millivolts as in Figure 2; resistance 4,000 ohms.

as was obtained with the German silver electrode. This is shown in Figures 2 and 3. (2) If the two metal plates were wrapped in a bandage soaked in salt solution, and were connected together by a sufficient length of bandage to make the resistance equal to that of the patient, for example, 4,000 ohms, then the application of a millivolt caused a prompt, maintained deflection with no signs of overshooting. This is identical with the curve obtained when two nonpolarizable cells are connected together by a bandage, and gives no evidence of polarization.⁴

It was further determined that this phenomenon is not due merely to the presence of a high resistance in the circuit, for if 10,000 ohms are introduced in series with the patient and galvanometer, it does

3. A full description of this electrode and of control tests will appear shortly.

4. See electrode article referred to in footnote 3.

not cause the phenomenon to appear in patients who do not otherwise show it.

What then is its explanation, and how can it be avoided? It was noticed that the phenomenon appeared chiefly or only in patients with a dry, rather bloodless type of skin, and, as has been said, only when the resistance as measured by the usual technique approached 2,000 ohms or more. It was also noticed that as the wet bandage remained longer about the extremity, the resistance as measured would gradually decrease, and with it the extent of the overshooting. Remembering that it is not the total resistance of the circuit which causes the appearance of this phenomenon, these facts lead to the conclusion that it is due to the local condition of the skin of the patient, either in the horny layer, or in the cutis as a whole.

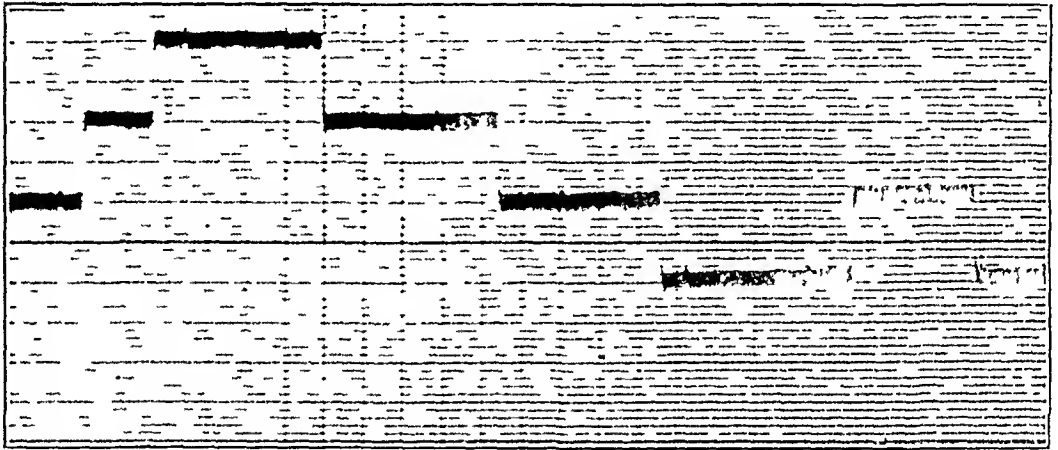


Fig. 5.—Obtained immediately after Figure 4, and with German silver electrodes, but the legs were first scrubbed with a hot salt solution and a hot bandage was applied; resistance 900 ohms.

What this condition is and how it acts to produce the effect noted, are at present undecided, though there seem to be two possibilities in each of these questions. The condition may be a dryness of the horny layer of the epidermis, or a vasoconstriction of the cutaneous vessels. The latter explanation is favored at present, because the phenomenon has been seen in several instances to pass off in such a very brief period of time, the resistance falling from 4,000 to 1,000 ohms, and the overshooting disappearing entirely in less than a minute, while in one instance the resistance rose just as suddenly from 1,200 to 4,500 ohms, and the overshooting, which had not been evident to the naked eye, became plainly so. Either of these conditions might cause the overshooting phenomenon by leading to polarization at the cutaneous surface or within its structure, but it is thought most likely that it is due to the skin functioning as a condenser surface, making the over-

shoot due to the charging of the condenser, and the slow decline due to its partial discharge through the resistance of the circuit.⁵

To avoid this source of error has been found comparatively easy, since its cause was approximated in this way, though before that time it was of common occurrence. The most important measure has been found to be the application of a hot bandage. The salt solution should be hot, preferably about 105 F., so that it stings the hand of the person applying the bandages. Of lesser importance has been found to be a thorough rubbing and wetting of the skin of the extremity before the bandage is applied. This alone will not usually suffice, but is an important accessory measure. In Figures 4 and 5 are records obtained before and after this treatment, showing the complete disappearance of the phenomenon.

45 East Sixty-Second Street.

5. This investigation has been discontinued owing to its extreme technicality, and to the fact that the source of error may be avoided with the knowledge now at our disposal.

STUDIES IN PROTEIN INTOXICATION

I. BLOOD COAGULATION *

HOWARD F. SHATTUCK, M.D.
NEW YORK

Since the first report on the use of human serum in certain diseases of the skin six years ago,¹ varying reports of its value for these conditions have appeared, many of them favorable. The work here reported is a continuation of that started by Swann,² and is concerned with further studies on the use of human serum in urticaria, especially regarding the effect of such serum on the coagulation factors of the blood in this condition.

Urticaria is believed by many to be an anaphylactic manifestation. Swann's² observation of the delayed coagulation of the blood in the case of urticaria he studied harmonizes with the conception of urticaria as a clinical manifestation of anaphylaxis, as in the latter condition the coagulation time of the whole blood is definitely delayed. Strickler³ found that eight out of ten cases of urticaria showed positive anaphylactic skin reactions, even though the results of these tests did not, as a rule, lead to therapeutic success. McBride and Schorer⁴ have pointed out the definite position of anaphylaxis as a cause of urticaria, assigning most cases to that cause.

Widal⁵ and his co-workers observed in their study of chronic urticaria that the ingestion of animal proteins to which the individual was sensitized, induced a series of disturbances definitely anaphylactic in character, namely, a fall in blood pressure, leukopenia, hypercoagulability (?) of the blood, profound lowering of the refractometric index, a rise of temperature and albuminuria. He concluded that these findings are caused by the passage of heterogeneous albumins into the blood.

The beneficial results obtained in some cases of urticaria from protein restriction in accordance with positive anaphylactic skin reactions, also lend weight to this view, as does the urticaria observed in indi-

* Submitted for publication April 12, 1917.

* From the Department of Pathology and the Medical Clinic, Presbyterian Hospital, Columbia University.

1. Mayer and Linser: *München. med. Wchnschr.*, 1910, **56**, 2757. Linser, P.: *Med. Klin.*, 1911, **7**, 1361; *Verhandl. d. Cong. f. inn. med.*, 1911, **28**, 125, and *Arch. f. Dermat. u. Syph.*, 1912, **113**, 701.

2. Swann, Arthur W.: *Jour. Am. Med. Assn.*, 1915, **64**, 737.

3. Strickler, Albert: *New York Med. Jour.*, 1916, **104**, 198.

4. McBride and Schorer: *Jour. Cutan. Dis.*, 1916, **34**, 70.

5. Widal, F.: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1914, **37**, 256.

viduals after the ingestion of certain food. The almost constant appearance of general urticaria in such a definite anaphylactic conditions as serum disease is also most suggestive.

These considerations led me to precede my study of the coagulation factors in urticaria and the influence on these factors of human serum therapy, with a study of the blood in experimental anaphylactic guinea-pigs and in cases of serum sickness in man.

Biedl and Kraus⁶ first observed the delay or loss of coagulability of the blood of dogs suffering from anaphylactic shock. The delay amounted to hours or days. Friedberger⁷ found that the coagulability of the guinea-pig's blood is lessened in anaphylaxis, but the diminution was slight as compared to that described by Biedl and Kraus⁶ in the dog, the delay being only a matter of minutes. Since then, other workers have observed the same condition, in this country, Pepper and Krumbhaar,⁸ Lee and Vincent,⁹ and recently Minot.¹⁰ Many have the impression that the delayed coagulability of the blood in anaphylactic animals is a matter of hours or days and of uniform occurrence in all anaphylactic animals. That this is not the case was shown first by Friedberger.⁷ Pepper and Krumbhaar's⁸ report of their work with dogs, in which the delay is most marked, shows that in only four out of seven cases reported did the delay amount to hours instead of minutes. Lee and Vincent⁹ give no figures. Minot's¹⁰ results were essentially the same. My work was confined to guinea-pigs.

The following was the technic used: Guinea-pigs were given a sensitizing intravenous injection of 0.5 c.c. of horse serum. Twenty-one days later a second 0.5 c.c. of horse serum was given and if anaphylactic shock developed, as shown by convulsions, dyspnea, weakness, involuntary defecation and urination, etc., blood was drawn from the heart and one portion put at once into sodium oxylate solution and later tested for the amount or efficiency of prothrombin, Howell's¹¹ method as described by Minot¹² being employed. Anti-thrombin was tested by the method described by Hess.¹³ A second portion was used to test the coagulation of the whole blood by the method described by Lee and White.¹⁴ Every effort was made to carry out the methods just mentioned, as exactly described by the various authors, with the utmost care as to the details of the technic.

As the blood of only one anaphylactic guinea-pig was tested on any one day, a normal nonanaphylactic guinea-pig's blood was used as a control in each case. The results of these studies appear in Table 1.

6. Biedl and Kraus: *Wien. klin. Wchnschr.*, 1909, **20**, 763.

7. Friedberger, E.: *Ztschr. f. Immunitätsforsch.*, 1909-1910, *Orig.* **4**, 636.

8. Pepper and Krumbhaar: *Jour. Infect. Dis.*, 1914, **14**, 476.

9. Lee and Vincent: *Jour. Med. Research*, 1915, **27**, 445.

10. Minot, G. R.: Personal communication.

11. Howell, W. H.: *THE ARCHIVES INT. MED.*, 1914, **13**, 76.

12. Minot, Denny and Davis: *THE ARCHIVES INT. MED.*, 1916, **17**, 101.

13. Hess, Alfred F.: *Jour. Exper. Med.*, 1915, **21**, 338.

14. Lee and White: *Am. Jour. Med. Sc.*, 1913, **145**, 495.

TABLE 1.—EFFECT OF HORSE SERUM INJECTIONS ON BLOOD OF NORMAL AND ANAPHYLACTIC GUINEA-PIGS

Exper.	Date	Experimental Animal	Coagulation Time of Whole Blood		Prothrombin		Antithrombin (Hess Method)					
							Control		3 Drops Anti-thrombin		5 Drops Anti-thrombin	
			Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.
1	3/ 3/16	Control	2	30	3	..	2	45	3	..	3	..
		Anaphylactic guinea-pig	6	..	9	8	30	9	..
2	3/15/16	Control	4	..	3	30	3	..	2	..	3	..
		Anaphylactic guinea-pig	16	30	14	6	..	6	..
3	3/15/16	Control	1	20	3	30	2	..	3	..	7	30
		Anaphylactic guinea-pig	21	..	19	30	9	30	15	..
4	3/24/16	Control	5	30	4	..	3	30	3	..	4	30
		Anaphylactic guinea-pig	12	..	14	30	3	30	3	30
5	3/26/16	Control	2	..	3	30	2	30	4	..	4	..
		Anaphylactic guinea-pig	9	30	8	7	..	9	30
6	4/ 3/16	Control	2	..	3	30	3	..	3	..	2	30
		Anaphylactic guinea-pig	30	30	24	30	7	..	9	30

A study of Table 1 shows that the coagulation time of the whole blood and the prothrombin time were uniformly delayed in the anaphylactic guinea-pigs. The determinations for antithrombin content were rather unsatisfactory and inconstant, as will be seen from the table, but there seemed to be a tendency to higher figures in the case of the anaphylactic blood. The unsatisfactory results may possibly be due to the fact that the Hess method is unsuitable for cases showing only slight variation in antithrombin content. Minot's¹⁵ results in similar studies were essentially the same, though in some instances he succeeded in obtaining anaphylactic guinea-pig's blood that did not clot for hours; in one instance only after twenty-four.

Various findings accompanying the delayed coagulability of the blood in anaphylactic animals have been reported as possibly explaining the phenomenon. Sirensky,¹⁵ in his work, reports that the fibrinogen and fibrin ferment were slightly decreased, while the calcium and magnesium content was unchanged. Conflicting reports occur as to the platelets. Achard and Aynaud¹⁶ found an associated disappearance of platelets, while Biedl and Kraus⁶ found the contrary. Some observers report a deficiency in the calcium content of the blood, but Pepper and Krumbhaar⁸ report opposite findings. The latter attribute the delay in

15. Sirensky. *Ztschr. f. Immunitätsforsch.*, 1910, **5**, 516.

16. Achard and Aynaud: *Compt. rend. Soc. de biol.*, 1909, **67**, 83.

coagulation to an abnormally small amount of thromboplastin, or to an excess of antithrombin. In support of the former theory they point out that the addition of calcium and thromboplastin solution constantly produced a more rapid coagulation than any other method. Somewhat suggestive of the latter view, though rather unsatisfactorily so, are the author's and Minot's findings of a tendency to high antithrombin figures in anaphylactic animal blood.

Studies were also made in the coagulation factors of the blood in known anaphylactic conditions in man, namely, in cases of serum sickness. Von Witzinger¹⁷ found in studying the effect of foreign serum injections in man on the coagulation of the blood, that the first injection was regularly followed by an acceleration of the coagulation, which subsided in twenty-four hours; also, that a second acceleration followed on the seventh, eighth, or tenth day after the injection, lasting a little longer than the first period. The reinjection of serum, however, was followed in five or six hours by a marked retardation of coagulation. This was most marked, he found, in cases in which the blood drawn directly from the vein was examined. His method of coagulation, however, can scarcely be said to be as accurate as those recently described, in view of the recent studies and theories of blood coagulation.

The author studied the coagulation time of the whole blood, the prothrombin time and antithrombin content in two cases of serum sickness following the injection of antipneumococcus serum in cases of lobar pneumonia, on the medical service of Dr. Longcope at the Presbyterian Hospital.

REPORT OF CASES

CASE 1.—C. M., aged 38, merchant, was admitted March 18, 1916; discharged April 24, 1916. The diagnosis was lobar pneumonia. There was a history of cough and fever for four days before admission. Examination showed physical signs of consolidation of lower lobe of the left lung. Blood culture and sputum both showed pneumococcus, Group I. The patient received 80 c.c. antipneumococcus serum, Group I, with 80 c.c. sterile saline twice, March 19, 1916, and two similar doses of serum and saline, March 20, 1916. Serum sickness developed, beginning March 27, 1916, with extensive general urticaria, erythema, enlarged lymph nodes, swelling and puffiness of face and eyes, and joint pains. With his blood later passive anaphylaxis was transferred to guinea-pigs and his skin reacted positively to horse serum. March 24, 1916, coagulation time of the whole blood (Lee and White method) was 11 minutes; control, 9 minutes; prothrombin time, 10 minutes; control, 9 minutes. April 8, 1916 (10 days after onset of serum sickness), the coagulation time of the whole blood was 24 minutes; control, 7 minutes; prothrombin time, 21 minutes; control, 8½ minutes. May 29, 1916, the coagulation time of the whole blood was 14 minutes; control, 8 minutes; prothrombin time, 12½ minutes; control, 7½ minutes.

CASE 2.—W. B., aged 38, was admitted Feb. 4, 1916; discharged March 10, 1916. Diagnosis, lobar pneumonia. There was a history of pain in the left side, with cough and fever for four days before admission. Examination showed

17. Von Witzinger, Oscar: *Ztschr. f. Kinderh.*, 1911-1912, 3, 211.

physical signs of consolidation of the left lower lobe. Blood culture was sterile. The sputum showed pneumococcus, Group I. The patient received 80 c.c. of antipneumococcus serum, Group I, with 80 c.c. sterile saline intravenously. Feb. 13, 1916, serum sickness developed; enlarged lymph nodes, joint pains, temperature, puffy face, diminished urine output and urticaria. Feb. 10, 1916, coagulation time of whole blood, 9 minutes; control, 9½ minutes; prothrombin time, 10 minutes; control 9 minutes. Feb. 16, 1916 (four days after development of serum sickness), coagulation time of whole blood, 18½ minutes; control, 6½ minutes; prothrombin time, 20 minutes; control, 9½ minutes. The patient was not obtained for further examination.

The tabulated results of these two cases appear in Table 2.

Turning now to the study of the coagulation factors in urticaria, the author studied the coagulation time of the whole blood, the prothrombin and antithrombin content, before and after treatment with

TABLE 2.—RESULTS OF BLOOD EXAMINATION IN CASES 1 AND 2 AFTER ANTI-PNEUMOCOCCUS SERUM, GROUP I

Case	Date	Time of Examination	Coagulation Time of Whole Blood		Prothrombin		Antithrombin (Hess Method)					
							Control		3 Drops Anti-thrombin		5 Drops Anti-thrombin	
			Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.
1. C. M.	3/24/16	3 days before serum sickness	11	..	10	..	9	30	10	..	10	..
		Control	9	..	9	9	30	11	..
	4/ 8/16	During serum sickness	24	..	21	..	8	30	10	30	10	30
		Control	7	..	8	30	10	..	11	30
	5/29/16	After serum sickness	14	..	12	30	8	..	8	..	9	30
		Control	8	..	7	30	8	30	8	30
2. W. B.	2/10/16	3 days before serum sickness	9	..	10	..	10	..	9	..	9	30
		Control	9	30	9	8	30	11	..
	2/16/16	During serum sickness	18	30	20	..	9	..	13	30	12	30
		Control	6	30	9	30	10	30	10	..

autogenous or heterogenous serum. Widal⁵ and his co-workers report a condition of hypercoagulability of the blood in a case of chronic urticaria after the ingestion of animal proteins. Wright and Paramore,¹⁸ however, report delayed coagulability of the blood in cases of urticaria, due, they believed, to a deficiency in calcium content. Nixon¹⁹ found the blood coagulation time delayed in his cases of urticaria tuberosa of Willan, a condition closely related to ordinary urticaria. Minot,¹⁰ in a study of three cases of severe urticaria, found the coagulation time of

18. Wright and Paramore: *Lancet*, London, 1905, 2, 1096.

19. Nixon, J. A.: *Quart. Jour. Med.*, 1916, 9, 245.

the blood and the prothrombin time normal in two cases and delayed in one. The antithrombin factor he found to be normal. The histories of the cases studied by the author follow, and later is found a table of the results obtained in the coagulation factors of the blood both before and after the treatment with autogenous or heterogenous serum.

CASE 3.—L. M. S., nurse, aged 30, was seen first May 15, 1916, complaining of severe attacks of hives for six months. The family history was negative and revealed no asthma, urticaria or hay-fever. The patient's appetite was good; she took two cups of coffee and one of tea a day. She had been constipated for four years. She worked hard and was frequently under a great deal of nervous strain. Menstruation was normal. She had had typhoid fever and an operation for appendicitis; otherwise, she had always been well; no hay-fever or asthma. Three years previously she had had a slight attack of hives of unknown cause. Prior to her present attack she ate anything and everything and it always agreed with her. In December, 1915, while nursing at the American Hospital in France, the patient developed a severe attack of hives, with itching and burning, involving the arms, ankles, abdomen and chest. The patient said it followed the eating of some queer meat, either horse or cat, and that some of the other nurses had hives as well. The patient used sodium bicarbonate and calcium lactate without relief. She returned to the United States in January, 1916. The hives continued in very severe form until May 15, when first seen. Many remedies were tried, but nothing but epinephrin subcutaneously gave relief, and that only temporarily. The patient weighed 121 pounds. She was rather nervous. Physical examination showed a dry, rough skin, without petechiae, but with several urticarial spots on the arms and shoulders. There was a moderate dermatographia. The color was good. Eyes, throat and teeth were normal. There were a few lymph nodes the size of peas in each posterior cervical chain. The lungs were clear and heart normal. Abdomen and extremities were negative. The blood pressure was 118-76. The blood showed: red blood cells, 4,800,000; hemoglobin, 85 per cent.; leukocytes, 9,600; polymorphs, 68 per cent.; lymphocytes, 32 per cent.; no eosinophils. The stool was soft, pasty, semiformed. Whole peas, cucumber seeds and spinach were easily recognized; no mucus, pus, or blood. Urobilin, slight; carbohydrate fermentation, slight; trypsin and amyllopsin, normal. Microscopically: starch particles, much cellulose; no increase in the total fat; no mucus, pus, or blood; no ova or parasites; many muscle fibers, with round corners and few striations; gram-negative organisms about 60 per cent. of the total number. Skin tests, intradermic method, were carried out by Dr. Frank Rackermann. Horse, sheep, dog, milk, beef, egg, cat, pig, rabbit, ragweed and goldenrod all gave negative results. The patient's serum, tested with horse and rabbit serum in various dilutions, gave no evidence of precipitins. Guinea-pig blood, sensitive to rabbit and horse serum, treated with patient's serum gave no precipitins. Coagulation time of whole blood (Lee and White method), twenty minutes; control, eight minutes; prothrombin time, seventeen minutes; control, nine minutes. For antithrombin contents and complete blood findings, see Table 3. The patient was put on an anticonstipation diet, excluding meat, milk, fish, eggs and raw fruit; calcium lactate and epinephrin hypodermatically as needed for severe attacks. At first she improved rapidly on this régime, but she relapsed in a few days and had several severe attacks of hives, involving usually the arms, legs, back and face. One of the attacks she thought was caused by eggs and another by lobster.

As the condition was improving very little, it was decided to treat the patient with serum intravenously. Accordingly, she was given varying amounts of serum obtained from two members of the house staff of the Presbyterian Hospital after the customary tests for Wassermann reaction, hemolysis, agglutination, etc., had been made. The patient belonged to Group II.

May 25, 15 c.c. serum were given intravenously. There was no reaction. The patient had slight headache. There were a few hives on the ankle that evening.

June 4, the patient had been having some hives off and on since May 25, relieved by epinephrin. She was still constipated. She was given 20 c.c. serum intravenously. There was no reaction. She was put on a diet that excluded meats, but not chicken, fish, eggs, milk, cheese and fruits, and was given a proprietary laxative twice a day. Coagulation time of the whole blood, 14 minutes; control, 9 minutes; prothrombin time, 17 minutes; control, 11 minutes.

June 14, hives less; only a few at a time and itched less; given 15 c.c. serum intravenously; no reaction. Eggs were added to the diet by request.

June 22, had had several severe attacks of hives, most severe since beginning treatment. Eggs and chicken were stopped again; given 18 c.c. serum intravenously. No reaction.

June 25, very few hives. "Feels much better generally." Fourteen c.c. serum given intravenously.

June 29, no hives since June 24; 15 c.c. serum given intravenously. (Sixth and last dose.)

September 12, the patient returned from a vacation in the Adirondacks. She reported that she had an occasional attack of hives—only two or three at a time—until July 4, and after that none at all. "No real hives since June 18." After the beginning of July the patient felt perfectly well; her nerves were much better and the constipation was relieved; she ate anything and everything with impunity. Coagulation time of the whole blood, 10 minutes; control, 8 minutes; prothrombin time, 9 minutes; control, 9½ minutes.

CASE 4.—J. S., aged 25, valet, was admitted to the Presbyterian Hospital March 1, 1916, complaining of headache and fever. Negative family history; no urticaria, eczema, asthma or hay-fever; had diphtheria at 6 and Neisser infection seven years prior to admission; otherwise he had been well. In January, 1916, the patient ate lobster salad while in Nassau-off-Florida, and during the following twenty-four hours had severe abdominal cramps, diarrhea and vomiting; also extensive eruption of hives involving face, abdomen, back and legs, and accompanied by unbearable itching. The gastro-intestinal symptoms subsided after twenty-four hours, but the hives continued off and on until admission. On admission he had a severe headache, felt weak and prostrated, and had had a severe eruption of hives for twenty-four hours. His temperature was 102 F., pulse 88, respirations 18. His appearance was that of the early stage of typhoid fever. The physical examination was negative, except for moderate enlargement of the inguinal and posterior cervical lymph nodes on both sides. Blood pressure, 124-80; weight, 108 pounds; blood culture was sterile; von Pirquet, negative; blood count showed leukocytes, on admission, 13,000, with 80 per cent. polynuclears, 20 per cent. lymphocytes; no eosinophils. Three days later when the temperature came down to normal the leukocytes were 5,200, with 54 per cent. polynuclears and 46 per cent. lymphocytes; no eosinophils. Lumbar puncture yielded negatives results. During his stay in the hospital the patient continued to have an extensive urticarial eruption, with occasional joint pains. He left the hospital after three days fully recovered except for the urticaria, which continued.

March 18, after leaving the hospital the patient was quite well except that the urticaria persisted. Coagulation time of the whole blood (Lee and White method), 14 minutes; control, 10 minutes; prothrombin time, 11 minutes; control, 11½ minutes.

April 5, had had joint pains from time to time and urticaria had been most severe of late, interfering with his sleep during the previous four nights. He was put on a strictly vegetarian diet; no meat, eggs, milk, cheese or fish. Serum treatment was started. Between April 14 and June 20 the patient received six doses of autogenous serum; the amount of each dose was from 12 c.c. to 20 c.c.

No reaction occurred. Autogenous serum was used because of difficulty in securing a regular donor, and because it seemed desirable to see if autogenous serum had the same effect as serum from other persons. During this time the patient had some joint pain and a varying amount of urticaria, until after the third dose of serum, May 25. After that he had no hives, and only occasional joint pain, until June 1; after that none. The patient was last seen Oct. 14, 1916. He had been perfectly well since June 1; no urticaria and no joint pains. Coagulation time of whole blood, $9\frac{1}{2}$ minutes; control, 7 minutes; prothrombin time, 10 minutes; control, $10\frac{1}{2}$ minutes. See Table 3.

CASE 5.—K. H., aged 17, woman, clerk, was first seen at the Presbyterian Dispensary, Sept. 16, 1915, complaining of indigestion and skin trouble lasting for six months. Negative family history; no urticaria, eczema, asthma, or hay-fever. She had had measles, diphtheria in 1914, and had received two doses of antitoxin. She says she had difficulty in breathing after antitoxin. She slept well and had a good appetite. Menstruation was normal and easy. Six months previously the patient began to have urticaria, with intense itching and dermatographia. The urticaria was general and constant when first seen, worse she thought, after eating eggs or meat. She was troubled considerably with stomach gas. The bowels were regular and urination normal. She was well developed and had a good color. The tongue was coated. Throat, heart, lungs and abdomen were negative. There was extensive urticarial eruption over the back, legs, abdomen and neck. The eyes and lips were not involved. She was put on a diet excluding meat and eggs, without benefit.

September 21, intradermic skin tests for sensitization were made by Dr. Rackermann. She gave a slight, though definite, reaction to horse serum; others were negative.

January 18, the urticaria had improved at times, then returned as severely as before. She had become discouraged about dieting and now ate what she pleased. Calcium lactate had no effect. She was relieved temporarily by epinephrin. The blood pressure was 110-76; red blood corpuscles, 4,600,000; hemoglobin, 88 per cent.; leukocytes, 9,600; polymorphs, 70 per cent.; lymphocytes, 28 per cent.; eosinophils, 2 per cent., and the coagulation time of the whole blood was 18 minutes; control, 9 minutes; prothrombin time, $18\frac{1}{2}$ minutes; control, $7\frac{1}{2}$ minutes.

February 6, the patient received 15 c.c. of autogenous serum, without immediate reaction. The patient could not be reached after this visit.

CASE 6.—E. D., aged 29, maid, was admitted to the medical service of the Presbyterian Hospital, June 24, 1916, where she remained, with short leaves, until Oct. 2, 1916. She complained of hives and swelling of her face for the previous three months. Family history negative; no asthma, hay-fever or eczema. As a child, she had had measles, scarlet fever and diphtheria without antitoxin. Her tonsils were removed fifteen years previously. She had had a slight attack of rheumatism five years previously. Her appetite was good, bowels regular, urination normal and habits good. She had always been nervous. Three months prior to admission she had had a severe gastro-intestinal attack, with nausea, vomiting and diarrhea, lasting twelve hours. The next morning her eyes and lips were puffy and she had some hives. Since then until admission she had had recurring swellings of her face, with severe urticaria, itching intolerably. She had "tried everything" without relief. Examination showed nothing abnormal except extensive urticaria and swollen eyelids and lips. The blood pressure was 126-80; urine, negative; hemoglobin, 90 per cent.; leukocytes, 7,000; polymorphs, 67 per cent.; lymphocytes, 33 per cent.; no eosinophils; weight, 111 pounds.

June 26, prothrombin time, 17 minutes; control, 8 minutes; coagulation time of whole blood, 14 minutes; control, 6 minutes. While in the hospital she had a curettage for a chronic leucorrhea. During this time she received four doses of heterogeneous human serum intravenously, each dose averaging 15 c.c.

August 25, patient returned to the hospital, having had an acute gastro-intestinal upset three days previously, and reporting that the hives and facial swellings were still as bad as ever. She was tried out with various dietetic restrictions, calcium lactate, epinephrin and atropin and colon irrigations—all without the slightest effect. Skin tests for sensitization to foreign proteins were always unsatisfactory, as the patient was continually having urticaria, which made the readings worthless. She received four doses of her own serum, 20 c.c. at a time. September 9, her coagulation time (whole blood) was 12½ minutes; control, 9 minutes; prothrombin time, 13 minutes; control, 10 minutes. The patient was seen in the dispensary at two-week intervals until December 1, and reported absolutely no improvement.

TABLE 3.—RESULTS ON BLOOD WITH HETEROGENEOUS AND AUTOGENOUS SERUM

Patient	Date	Coagulation Time of Whole Blood		Prothrombin		Antithrombin (Hess Method)					
						Control		3 Drops Anti-thrombin		5 Drops Anti-thrombin	
		Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.
3. L. M. S.	4/19/16 No treatment with serum	20	..	17	..	7	..	6	30	9	30
	Control.....	8	..	9	7	..	7	30
	5/29/16 2 doses serum...	18	..	14	..	8	30	9	..	14	30
	Control.....	10	..	7	10	30	11	..
	9/12/16 After 6 doses serum	10	..	9	..	10	30	8	..	10	..
	Control.....	8	..	9	30	10	..	11	30
4. J. S.	4/14/16 No treatment...	14	..	11	..	10	..	12	..	11	30
	Control.....	10	..	11	30	10	..	11	..
	10/14/16 After 6 doses serum	9	30	10	..	7	..	7	30	8	30
	Control.....	7	..	10	30	7	..	8	..
5. K. H.	1/18/16.....	18	..	18	30
	Control.....	9	..	7	30
6. E. D.	6/26/16.....	14	..	17
	Control.....	6	..	8
	9/ 9/16.....	12	30	13
	Control.....	9	..	10
7. J. I.	9/21/16.....	14	..	15	30	9	..	8	30	9	..
	Control.....	10	..	9	9	..	10	30
	11/ 2/16 After serum.....	12	..	10
	Control.....	9	..	10

CASE 7.—Mrs. J. I., aged 30, teacher, was admitted to the Presbyterian Hospital, Sept. 1, 1916; discharged Sept. 30, 1916. Diagnosis, angioneurotic edema and urticaria. Her complaint was hives and facial swellings for six weeks. The family history was negative for urticaria, eczema, asthma and hay-fever. She had had the usual children's diseases, including diphtheria, without antitoxin. Two years prior to admission both ovaries were removed for cysts, and she had been troubled with hot flushes and headaches since then. She tired easily; appetite was good; bowels regular; urination normal. She had had no children; no miscarriages. Fifteen years prior to admission the patient had an attack of angioneurotic edema and urticaria like the present attack; it lasted for two years, and she had no further trouble until the present attack. For

one month the patient had had swellings of lips and eyes and severe general urticaria, not influenced by dieting or medication. During the previous two weeks the patient had noticed small black and blue spots over her thighs and legs. She was well nourished and quite nervous. The left eye was swollen almost shut and she had some urticarial wheels scattered over back and abdomen. There were a few purpuric spots scattered over her thighs and legs. Otherwise, the examination showed nothing abnormal. The hemoglobin was 86 per cent.; leukocytes, 6,600; polymorphs, 66 per cent.; lymphocytes, 34 per cent.; no eosinophils. Coagulation time of whole blood, 14 minutes; control, 9½ minutes; prothrombin time, 13½ minutes; control, 8 minutes. She was given a diet without fish, milk, eggs, meat or cheese, and calcium lactate. She rapidly improved, but thought that when lamb chops were later added she became worse. During her stay in the hospital she was given two doses of autogenous serum (20 c.c. each). Intracutaneous tests for sensitization showed positive reaction to phaseolin (beans), beef and pig. She was put on a diet that excluded these articles and discharged. Following her discharge she improved markedly, had no swellings of her face and "the hives had been much better." She had one severe attack after eating beef, but ate pork with impunity.

November 2, coagulation time of whole blood, 12 minutes; control, 9 minutes; prothrombin time, 10 minutes; control, 10 minutes.

Nothing was found to explain why the delayed coagulation time of the whole blood and the delayed prothrombin time disappeared with an approach to normal figures in three out of the four cases of urticaria treated with serum. If, as some²⁰ think, by the introduction of autogenous defibrinated blood or blood serum an appropriate antigen is introduced to create the appropriate antibodies for the production of active immunization, then it is possible that the anaphylactic state is overcome, and hence the coagulation factors of the blood change to normal. But, as we are dealing with so complex and so little understood a substance as blood serum, no definite conclusion can be reached.

The author is not prepared to assert anything at this time as to the therapeutic value of human serum in clinical anaphylaxis in man. This problem is now being investigated, and the results will be reported at another time.

SUMMARY

1. Studies with anaphylactic guinea-pig's blood showed a delay in the coagulation time of the whole blood and in the prothrombin time. Determinations of antithrombin content were inconstant and unsatisfactory, but there seemed to be a tendency to higher figures in the case of the anaphylactic blood.

2. Studies with the blood of patients suffering from serum sickness showed a marked delay in the coagulation time of the whole blood, and of the prothrombin time during the serum sickness, with a later fall to nearly, but not entirely, normal figures for both after the disappearance of the serum sickness. The results with the antithrombin content were inconclusive.

3. Studies of the blood of patients suffering with chronic urticaria showed a delayed coagulation time and prothrombin time in four out of five cases, with an approach to normal figures after the patients had been treated intravenously with autogenous or heterogenous serum in three cases out of four.

The funds necessary to carry out the foregoing study were supplied by Mrs. Arthur W. Swann, in memory of the late Dr. Arthur W. Swann. I wish to thank Dr. W. G. McCallum, Dr. Warfield T. Longcope and Dr. Albert R. Lamb for their constant assistance and cooperation.

771 Madison Avenue.

EMETIN DIARRHEA—CLINICAL AND EXPERIMENTAL

A. R. KILGORE, M.D.

AND

J. H. LIU, M.D.

SHANGHAI, CHINA

It is well known that, in large doses, emetin hydrochlorid gives rise to a hemorrhagic gastro-enteritis in experimental animals. That it produces a bloody diarrhea not rarely in the course of its clinical use is coming to be recognized, though in an exhaustive review of the literature published last year¹ only seven cases were collected. A number of unpublished cases occurring in China have come to our attention through personal communications. It seems to us to present a real danger, well worth more discussion than it has received.

The difficulty in the recognition of diarrhea from emetin, as well as its danger, is due to the fact that it occurs in the course of treatment for amebic dysentery and that the symptoms and the gross appearance of the stools in emetin diarrhea are almost indistinguishable from those in amebic dysentery. The patient receives daily doses of emetin and for a few days improves and the amebas disappear from the stools, which become more or less normal. Then the diarrhea becomes worse, with reappearance of blood and mucus in the stools. Mistaking this condition for a relapse of the dysentery, the emetin is pushed, which only increases the diarrhea, and if the condition is not recognized serious results may easily follow.

The following case reports will perhaps best illustrate the condition. They were all cases in private practice or seen in consultation by one of us.

REPORT OF CASES

CASE 1.—A boy of 6 began to have bloody diarrhea while on a Yangtze River steamer, so that his stools were not examined microscopically. They had the gross appearance, however, of amebic dysentery stools and he was given emetin in 15 mg. ($\frac{1}{4}$ gr.) daily subcutaneous doses for two days, and then one dose of 30 mg. ($\frac{1}{2}$ gr.). The stools decreased to one or two a day and were fairly normal in appearance. On the fourth day he was given 65 mg. (1 gr.), and the following day had a return of his diarrhea—five stools with blood and mucus; no amebas found. The emetin was stopped and he began to improve at once, was well within a week and had remained well when last reported five weeks later.

* Submitted for publication April 6, 1917.

* From the Harvard Medical School in China and the Red Cross General Hospital.

1. Levy and Rowntree: On the Toxicity of Various Commercial Preparations of Emetin Hydrochlorid, *THE ARCHIVES INT. MED.*, 1916, **17**, 420.

CASE 2.—A boy of 18 months had a typical bloody diarrhea, but amebas were not recognized with certainty (in a cold specimen). He was given emetin 20 mg. ($\frac{1}{3}$ gr.) a day for five days, with marked improvement during the first three days, in the frequency and character of the stools, though they did not become quite normal. On the fourth day the diarrhea was worse, and on the fifth day still worse, with stools every half hour consisting almost entirely of blood and mucus and passed with evident pain. No emetin was given after the fifth day. Improvement began at once and within four days the diarrhea had practically ceased. Six months later he had had no recurrence.

CASE 3.—A Chinese boy of 10 had bloody diarrhea with amebas in the stools. He was seen by two Chinese Western-trained practitioners and was given injections of emetin amounting to 450 mg. (7 gr.) in the course of six days. At the end of this time he was getting very much worse and was passing stools two or three times an hour. There was great prostration and a continued fever of 102 to 104 F. The stools consisted entirely of blood, pus and mucus, apparently not at all different from those passed before treatment was begun, except that no amebas were found. Consultation with one of us resulted in the diagnosis of emetin diarrhea and the discontinuance of the emetin. The patient began to improve at once and with administration of bismuth by mouth and tannic acid irrigations per rectum, he recovered completely in the course of ten days.

It may be noted that this last case differs from the others in that there was no temporary improvement after the first two or three injections of emetin. We attribute this to the fact that the dosage was so overwhelmingly large that the emetin diarrhea was already started before the amebas had disappeared.

In only the last case was any change in the dietary or other treatment made when the emetin was discontinued. The last patient was in such bad condition that tannic acid irrigations were given.

Only one case of human emetin poisoning has come to necropsy and been reported—that of Levy and Rowntree¹—and in this case there had been no diarrhea for five days before death, the gastrointestinal tract showing only a "slight flushing of the mucosa" in the lower part of the ileum. We have seen one fatal case—a child of 18 months—in which there was, first, improvement with disappearance of amebas from the stools, later increase in the diarrhea. The emetin was pushed instead of stopped and the case went on to fatal termination. This case is not included in our list of reported cases because it was impossible to secure a necropsy and prove the diagnosis. We hope not to have opportunity to secure a human necropsy on this condition and are therefore dependent on experimental animals for a study of its pathology.

EXPERIMENTS

Hemorrhagic gastro-enteritis has been produced in dogs with emetin by a number of investigators.² Our experiments were under-

2. Levy and Rowntree: See Footnote 1. Dale: A Preliminary Note on Chronic Poisoning with Emetin, *Brit. Med. Jour.*, Dec. 18, 1915, p. 895. Pellini and Wallace: Pharmacology of Emetin, *Am. Jour. Med. Sc.*, 1916, **152**, 325.

taken primarily in an effort to produce peripheral neuritis³ rather than gastro-enteritis, but they have furnished an opportunity to corroborate, and perhaps to extend somewhat, the observations published by others on the latter condition.

Thirty dogs were used in the experiments on peripheral neuritis. A somewhat more detailed study of the gross and microscopic necropsy findings on the first thirteen of these dogs forms the basis of this report.

Of these thirteen dogs, eleven were given emetin and two were kept in adjoining kennels on the same food as controls. The doses of emetin given varied from 1 to 8 mg. per kilo of body weight—averaging 2 to 2.5 mg. per kilo. The doses were all given subcutaneously, daily or every other day.⁴

There was considerable variation in the number and size of the doses required to kill the animals. The symptoms shown and the pathologic findings depended on this factor of individual variation more than on the size and number of doses.

Typically, after several doses, the animals gradually became listless, then began to refuse food and to show signs of increasing weakness, progressing to death. Death frequently occurred from three to six days after the last dose of emetin had been given. In fact, only one dog recovered after the development of definite symptoms, even though the emetin was discontinued at once.

Nine of the eleven dogs that died from emetin were observed to have bloody stools, or showed bloody fluid in the gastro-intestinal tract at necropsy. Only three were known to vomit, the vomitus in one instance containing a small amount of blood (by guaiac test).

PATHOLOGY

The *pathology* was that of hemorrhage throughout. The distribution and extent varied somewhat, but little else of significance was found.

The *peritoneum* in one case showed hemorrhagic infiltration of both parietal and visceral layers ventrally over an area half the size

3. These experiments were stimulated by the observation of a number of cases of peripheral neuritis seen in human beings and reported by one of us (Kilgore, A. R.: *Peripheral Neuritis Following Emetin Treatment of Amebic Dysentery*, Boston Med. and Surg. Jour., 1916, **175**, 380). Observations on the peripheral neuritis produced in dogs will be published in a separate communication.

4. A dose of 2 mg. per kilo for a man of 65 kilos (143 pounds) would be 130 mg. (2 gr.). This is perhaps the upper limit of the doses usually given clinically. The preparation used in all the experiments was Parke, Davis & Co.'s hypodermic tablets.



Fig. 1.—Intestine, showing the characteristic location of hemorrhages at the tip of a fold, and the superficial distribution in, as well as under, the mucosa.



Fig. 2.—Mesenteric lymph node, showing hemorrhage filling the lymph sinuses in the center of the node.

of one's palm. Another case showed many bright petechiae over the surface of the lower large bowel.

The *gastro-intestinal tract* typically contained more or less bloody fluid and mucus, sometimes in the upper and sometimes in the lower part of the tract. In two instances the intestine was nearly filled with dark red fluid from the stomach to the rectum. All the dogs showed submucous hemorrhages of varying character and distribution, with a tendency to be most marked in the upper small bowel and also in the first part of the colon. In one dog the mucous membrane was lifted off the submucosa in two places by hemorrhages 3 to 4 mm. in diameter. The typical lesions, however, were petechiae, commonest in the duodenum and upper jejunum and in the proximal colon, but often extending from the pyloric half of the stomach to the rectum. The petechiae tended to pick out the tips of the folds of mucous membrane, giving a very curious striated appearance, and in three instances the edge of the ileo-cecal valve was crowded with petechiae. Microscopically, the hemorrhages were found to be very superficial, occurring not only under the mucosa, but in it between the gland tubules (Fig. 1).

In several of the dogs a varying number of punched-out depressions, 4 to 6 mm. in diameter, with smooth, rather convex bases, were found in the mucosa chiefly of the upper small bowel. These were also found in the normal control dogs and were seen microscopically to be lymphoid patches. In two of the emetin dogs several of these were hemorrhagic. In some descriptions "ulcers" have been mentioned, corresponding in appearance and distribution very closely with these lymphoid patches. No true ulcers were observed in any of the dogs in this series.

The *mesenteric glands* in all the dogs, including the controls were very large, up to 2 or 3 cm. in length and 5 to 10 mm. thick. They usually showed on cross section brownish centers and white peripheries (of lymph follicles). In seven of the eleven emetin dogs, the mesenteric glands exuded blood on section and in two dogs similar popliteal glands were found.

Microscopically, the hemorrhages were found to be confined chiefly to the lymph sinuses. The cortices together with the lymph follicles showed no changes in structure from those in the control dogs. The lymph spaces showed abundant collections of blood, in most cases quite fresh, which, staining a bright red, stood in striking contrast to the blue-staining medullary cords which are surrounded by them (Fig. 2). In a few cases in which there had been hemorrhage apparently some time before death, the lymph sinuses contained large numbers of endothelial leukocytes, many of which showed their phagocytic nature by the incorporation of red blood corpuscles or blood pigment.

The *liver* was in a few instances quite congested both grossly and microscopically, the congestion of the sinusoids showing no characteristic distribution with reference to the lobules. Petechiae under the peritoneal surface of the liver were found, confined to small areas, in one instance.

The *spleen* showed hemorrhages in all of the emetin dogs. It is very hard to say whether there was increase in the size of the organ, but there was apparently congestion in each case. The consistence of all the spleens, including the controls, was rather firm, but the ones which showed the most hemorrhage were softer. Microscopically, the hemorrhages were found in all parts of the pulp, but the periphery was spared in only two cases, and in six the hemorrhage was most prominent or entirely confined to this region (Fig. 3). The splenic corpuscles showed nothing pathologic in themselves, but were sometimes encroached on by hemorrhages. In cases in which the hemorrhage had apparently existed for some time there was a great increase in the number of phagocytic endothelial leukocytes and a concomitant proliferation of the connective tissue cells of the reticulum. Lymphocytes were comparatively scarce in all the spleens except in the vicinity of and forming the splenic corpuscles.

The *kidneys* showed a moderate degree of congestion in most cases and occasional small hemorrhages in the medulla. The glomeruli and tubules were not markedly affected.

The *pancreas*, *adrenals*, *lungs* and *heart* showed nothing of note.

In two young dogs the *thymus* was found to be of large size, purple in color and dripping blood on section. In one of these and in one other dog petechiae were found in the fat of the anterior mediastinum. A section of thymus is shown in Fig. 4.

The nervous system showed no obvious lesions.

SUMMARY

Three cases are reported in which the diagnosis of emetin diarrhea, produced in the course of treatment for amebic dysentery, is reasonably certain. Recovery was prompt on discontinuing the emetin. The authors have seen a fourth case, terminating fatally, in which the same diagnosis was made, but have not reported this case in detail on account of failure to secure a necropsy.

All of these cases were in children and all had received doses considerably larger than would be proportionate on a basis of 65 mg. (1 gr.) for an adult. This fact is especially interesting in view of the opinion not infrequently held that children are more resistant to emetin than adults. It is our present practice to give doses of 65 mg. (subcutaneously or intravenously) to adults and to graduate doses for chil-

dren proportionately, watching carefully for any increase in the diarrhea which might be due to emetin.

Experiments of others and those reported here furnish abundant evidence of the tendency of emetin to produce in dogs a hemorrhagic gastro-enteritis with hemorrhages in the lymph glands, spleen, kidneys, thymus, etc., ultimately resulting in death, even if the emetin be stopped as soon as definite symptoms are observed.

STUDIES ON THE OXIDASE REACTION OF THE CELLS IN NORMAL AND LEUKEMIC BLOOD*

N. ROSENTHAL, M.D.

NEW YORK

The oxidase reaction is considered specific for the myeloid series of cells (polymorphonuclears, myelocytes and myeloblasts) and its performance is briefly summarized as follows: A normal blood smear is fixed in formaldehyd vapor and then flooded with a mixture of alphanaphthol (1 per cent.) and dimethylparaphenylenediamin (1 per cent.) for a few minutes. On examination the smear will show the presence of blue granules in the polymorphonuclear cells and no granules in the lymphocytes. The blue granules are supposed to be due to the synthesis of indophenol blue from the oxidation of alphanaphthol and dimethylparaphenylenediamin, the condensation of the molecules being effected by an oxidizing ferment or oxidase, which is present in the premature and mature bone marrow cells.

During the course of an investigation of the classification of the leukocytes in normal and abnormal blood I have had occasion to perform the oxidase reaction for the demonstration of the oxidase granules in the various types of blood cells, both in normal and leukemic blood. The occurrence of these granules in the myeloid series of cells has become an important method of distinguishing between the lymphoid and myeloid types of leukemia, especially when the character of the mononucleated cells is difficult to determine with polychromatic staining. The reaction is also considered of great importance in view of the fact that conflicting statements exist concerning the reaction on certain blood cells, which may possibly be lymphoid or histogenous in origin, and that certain definite myeloid cells fail to show the oxidase granules.

The history and theories of the oxidase reaction have been well reviewed by Loele¹ and Battelli and Stern,² to whom the reader is referred for interesting information concerning the oxidative phenomena of the cells. It is my purpose to give only a summary of the various theories and the important methods of the microchemical demonstration of the oxidizing ferments of the blood cells.

The two main oxidizing ferments of the blood cells are the oxidases and the peroxidases. The former can break up oxygen (O_2) into

* Submitted for publication April 6, 1917.

* From the Pathological Laboratory, Mount Sinai Hospital.

1. Loele, W.: *Ergebn. d. allg. Path.*, 1913, **16**, 760.

2. Battelli and Stern: *Ergebn. d. Physiol.*, 1912, **12**, 96.

nascent oxygen (O) in order to oxidize a substance, and the latter is capable of breaking up hydrogen peroxid into water and nascent oxygen, which becomes available for oxidative processes. The true nature of these ferments is still unknown, and it is problematical whether the oxidase and peroxidase reaction of the blood is due to the action of a ferment or to a biochemical side chain.

According to Loele,¹ the oxidases or oxidase granules can be shown in the blood cells in three ways:

A. Acceleration of a dye synthesis, by an oxidative process within the cell.

B. The acceleration of dye formation outside of the cell by means of an intracellular oxidative substance.

C. Oxidation of a reduced dye such as methylene white.

A. *Acceleration of a Dye Synthesis, by an Oxidative Process Within the Cell.*—This depends, according to Loele, on a phenol reaction, or polyphenoloxidase, according to Battelli and Stern.² The cellular granules in this reaction appear as yellow, brown, violet or black, or the cytoplasm may show a diffuse coloration. Various phenols such as epinephrin, resorcin, alphanaphthol, pyrogallol, etc., in weak alkaline solution, are oxidized in this manner.

Three important methods are used in such oxidase reactions, as follows:

1. The epinephrin reaction of Kreibich.³ The oxidase granules of the blood are stained by epinephrin (1-1,000).

2. Alphanaphthol-gentian-violet method of Loele.⁴ Beautiful and relatively permanent preparations are obtained by this method, but it does not show as many oxidase cells as some of the other methods cited.

3. Alphanaphthol-pyronin method of Graham.⁵ This method was carefully studied in comparison with other methods and was found to be excellent. The details of the procedure will be described later. The method depends on the use of hydrogen peroxid and may possibly be an indicator of peroxidases. The reaction also depends on the acidophilic properties of the granules, since I have found that the reaction is not obtained in basophil cells.

B. *The Acceleration of Dye Formation Outside of the Cell by Means of an Intracellular Oxidative Substance.*—The indophenol-blue synthesis from the oxidation of alphanaphthol and dimethylparaphenylenediamin is an example of this reaction. This was first used by

3. Kreibich, C.: Wien. klin. Wchnschr., 1910, **23**, 701.

4. Loele, W.: Folia haemat., 1914, **18**, 581.

5. Graham, C. S.: Jour. Med. Research, 1916, **35**, 231.

Ehrlich⁶ who injected a mixture of alphanaphthol and paraphenylenediamin intravenously and noticed a marked indophenol-blue coloration of the brain, heart and diaphragm, but very little indophenol in the liver, muscles and kidneys. The blood did not show any indolphenol. Röhman and Spitzer⁷ (after whom the indophenol reaction is named) found that indophenol is produced from a mixture of alphanaphthol and paraphenylenediamin when exposed to the air, but the reaction is hastened when macerated liver is added to the reagents. Winkler⁸ used the alphanaphthol-paraphenylenediamin reaction on gonorrheal smears and found that such smears become blue. He attributed an oxidase reaction to both myeloid and lymphoid cells, and also to erythrocytes in anemia. Schultze⁹ introduced this reaction for tissue sections and blood smears as a diagnostic method for the recognition of myeloid leukemias, and found that only myeloid cells react to the alphanaphthol and dimethylparaphenylenediamin. Previous to the introduction of the indophenol reaction, the guaiac reaction (Brandenburg,¹⁰ Meyer and Heineke¹¹) was used to a large extent. The serum of myeloid leukemias oxidizes guaiac to a blue color even without the presence of hydrogen peroxid; normal and lymphoid leukemic serums do not oxidize it. Klein,¹² however, called attention to certain lymphatic leukemias which give the characteristic guaiac reaction.

METHODS

The most important methods of carrying out the indophenol or oxidase reaction are as follows. Most of the authors recommend formaldehyd vapor as a fixative.

I. The three methods of Schultze:¹³

- A. 1. Alphanaphthol (1 per cent. boiled in water and sufficient potassium hydroxid added to dissolve it).
2. Dimethylparaphenylenediamin, 1 per cent. According to Pappenheim and Nakano,¹⁴ this is good for eosinophils, but his following two methods are preferable for polynuclear neutrophils. Winkler⁸ uses sodium carbonate instead of potassium hydroxid.
- B. 1. Mikrocidin (Betanaphthol sodium), 2 per cent.
2. Dimethylparaphenylenediamin hydrochlorid, 1 per cent.
- C. 1. Alphanaphthol as in A.
2. Paranitrosodimethylanilin, 1 per cent.

-
6. Ehrlich, P.: *Das Saurstoffbedürfnis des Organismus*, Berlin, 1885.
 7. Röhman and Spitzer: *Chem. Ber.*, 1895, **28**, 567.
 8. Winkler, F.: *Folia haemat.*, 1907, **4**, 323.
 9. Schultze, W. H.: *Beitr. z. path. Anat. u. z. allg. Path.* (Ziegler's), 1909, **45**, 127.
 10. Brandenburg, K.: *München. med. Wchnschr.*, 1900, **42**, 183.
 11. Meyer, E., and Heineke: *München. med. Wchnschr.*, 1903, **52**, 1489.
 12. Klein, Stanislaus: *Folia haemat.*, 1904, **1**, 71.
 13. Schultze, W. H.: *München. med. Wchnschr.*, 1909, **56**, 167; 1910, **57**, 2171.
 14. Pappenheim and Nakano: *Folia haemat.*, 1912, **14**, 260. Nakano, J.: *Folia haemat.*, 1913, **15**, 123.

The solutions of *A* need not be fresh and are used in succession, but the *B* and *C* solutions must be freshly prepared and mixed before they are applied to the blood smear.

II. Von Gierke's method:¹⁵

Both reagents (Schultze's method *A*) are dissolved in physiologic saline solution. Pappenheim and Nakano¹⁶ consider it a good stain for neutrophilic granules, especially after osmic acid fixation. Von Gierke, using his method on fresh tissue, identifies more oxidase cells than those found in tissues fixed with formaldehyd. The additional cells are due to labile oxidases, which are destroyed by formaldehyd.

III. Fiessinger and Rudowska's¹⁰ method:

Alphanaphthol, 1 to 4,000.

Dimethylparaphenylenediamin, 1 to 1,000.

This proves to be economical in the use of reagents and adequate for the rapid differentiation and rough estimate of the number of oxidase cells present in the blood smear.

IV. Dunn's¹⁷ method:

Fix in osmic acid, 1 per cent., five seconds.

Wash in running water five minutes.

Flood slide for five minutes with a mixture of equal parts of alphanaphthol, sat aq. sol., and dimethylparaphenylenediamin, 0.20 per cent. aq. sol.

The method is excellent. The slide can be directly examined with the oil immersion lens, but the granules begin to fade within one-half hour. The method, however, often fails to show granules in myeloblasts when these can be identified with other methods.

V. Pappenheim's method. The steps of the procedure will be described later.

C. Oxidation of a Reduced Dye Such as Methylene White.—This method was applied by Unna¹⁸ to demonstrate oxidizing substances. The main sources of the oxidases with this method are the nuclei and basophil particles; lipoids react after treatment with formaldehyd.

The nature of the oxidizing substance is still unknown. The various reactions for the demonstration of these oxidizing substances depend on receptors in the cells, which are able to fix the oxidized or synthetized coloring material. The receptors must possess a surplus of oxidases, for it has been shown that reductases are also present in the cell (Schultze,¹³ Unna¹⁹). The presence of both reductases and oxidases in well balanced proportions probably accounts for the failure of certain structures to stain with the synthetized color reagents. Schultze and Winkler consider the oxidizing substance of the cell to be a ferment (oxidase or peroxidase); Dietrich²⁰ believes that the reaction

15. Von Gierke, E.: München. med. Wchnschr., 1911, **57**, 2171.

16. Fiessinger, N., and Rudowska, L.: Arch. de méd. exper. et d'anat. Path., 1912, **24**, 585.

17. Dunn, J. S.: Jour. Path. and Bacteriol., 1911, **15**, 20; Quart. Jour. Med., 1913, **6**, 293.

18. Unna, P. G.: Arch. f. mikr. Anat., 1911, **78**.

19. Unna, P. G., and Golodetz, C.: Dermat. Studien, 1912, **22**.

20. Dietrich, A.: Zentralbl. f. Path., 1908, **19**, 3.

depends on the lipoids. Herxheimer²¹ recommends indophenol in 70 per cent. alcohol as an excellent blue stain for fat. Ikeda²² found that the granules of the cells of the submaxillary gland, which show a distinct oxidase reaction, also stained by Smith's method for fat. Neutrophilic granules, however, after prolonged treatment with alcohol, ether and chloroform can still show a marked oxidase reaction. It is possible that the oxidase reaction of the endothelial cells (Ikeda²²), the transitionals and the large mononuclears, depends on lipoidal particles which often cannot be identified with the ordinary blood stains. Loele attributes the reaction to a phenophil substance in the cell.

The different methods advocated for blood films were investigated, but most of them proved inadequate for the study of the types of cells involved in the reaction. Some of the methods also proved to be inconstant and often failed to work. The Pappenheim and Loele and Graham methods proved to be excellent for routine work. The cells, by employing these methods, could be examined directly through cedar oil (obviating the use of cover glasses). Another advantage is the fact that the solutions for use in the reaction need not be freshly prepared. Fixation with osmic acid (1 per cent.), alcohol (95 per cent.), or, preferably, alcohol-formaldehyd (9 to 1), did not interfere with the oxidase reaction (Dunn,¹⁷ Graham⁵), but, on the contrary, intensified it (Klopfer²³). The Loele method failed to identify as many oxidase cells as Pappenheim's or Dunn's methods (similar to the experience of Pappenheim and Nakano), and the method of Graham was substituted for it.

The Pappenheim method gave reliable results, and, furthermore, proved to be extremely advantageous for the study of the cells with the oil immersion lens. The following is a schematic outline of the method employed:

Pappenheim's Method (Author's Modification):

1. Fix with alcohol (95 per cent.), formaldehyd (40 per cent.), (9 parts of the former to 1 part of the latter) two minutes. Formaldehyd solution alone or osmic acid (1 per cent.), as in Dunn's method, can also be used.
2.

Alphanaphthol	1.0	}	Two minutes.
Absolute alcohol	30.0		
Distilled water	100.0		
Concentrated ammonia	0.3		
3. Follow with 1 per cent. solution of paraphenylenediamin two minutes.
4. Counter stain with aq. pyronin (1 per cent.) thirty seconds.
5. Blot and examine with oil immersion lens.

Graham's Method.—Graham's alpha-pyronin method corresponded to the results obtained with the Pappenheim oxidase method. Beautiful pictures are

21. Schmorl, G.: Untersuchungenmethoden, Leipzig, 1914, p. 161.

22. Ikeda, Y.: Verhandl. der Japan path. Gessellsch., 1913, p. 86.

23. Klopfer, A.: Ztschr. f. exper. Path. u. Therap., 1912, **11**, 467.

obtained when the steps are carefully carried out as described by Graham, and the slides resemble blood films stained with Jenner's methylene blue eosin. The staining is done as follows:

1. Fix with alcohol-formaldehyd (9-1) two minutes.
2. Flood slide with

Alpha naphthol	1.0	} Five minutes.
Alcohol, 40 per cent.....	100.0	
Hydrogen dioxid	0.2	
3. Wash in running water fifteen minutes.
4. Stain with pyronin..... 0.5 }
 Anilin oil 4.0 } Two minutes.
 Alcohol, 40 per cent..... 96.0 }
5. Wash in water.
6. Stain with methylene blue BX 0.5 per cent. thirty seconds.

I have found that Loeffler's alkaline methylene blue may be substituted for the methylene blue BX, if the latter cannot be obtained.

7. Wash in water; blot.

The appearance of the oxidase granules in the various cells of normal blood are shown in Table 1:

TABLE 1.—NORMAL BLOOD

Series	Type of Cell	Pappenheim's Oxydase Stain; Counter-Stained with Pyronin	Graham's Stain
Myeloid.....	Poly. neutrophil	Numerous blue to violet granules; varying in size	Numerous red granules
	Poly. eosinophil	Large blue granules....	Numerous red granules (circles)
	Poly. basophil	Blue granules present; irregular in shape.	Granules unstained by pyronin and methylene blue
	Blood platelets; erythrocytes	No granules	No granules
Lymphoid.....	Lymphocytes	No granules; very rarely small black granules	No granules
	Plasma cells (irritation forms)	No granules	No granules
Monocytic.....	Transitionals	Few scattered black or violet granules (never blue) or no granules	No granules or few red granules varying in size
	Large mononuclears	No granules or few black; occasionally few blue granules (myeloblasts?)	No granules, or a few red granules

THE OXIDASE GRANULES OF NORMAL BLOOD CELLS

The oxidase reaction in normal cells has been studied by a large number of investigators, who agree fairly well in regard to the marked reaction of the polymorphonuclear neutrophils, eosinophils and basophils. Pappenheim failed to obtain an oxidase reaction in the tissue basophilic cells. The eosinophils show the most marked reaction, but the neutrophils also show fairly large granules. Dunn¹⁷ was unable to demonstrate oxidase granules in lymphocytes, even after long contact with the staining mixture. Sapegno²⁴ found oxidase granules in lym-

24. Sapegno, M.: *Pathologica*, 1908, **1**, 722; 1910, **2**, 131; *Folia haemat.*, 1910, **9** (Zentral-Organ), 389.

phocytes and Fiessinger and Rudowska¹⁶ noticed a slight indophenol reaction in the lymphocytes and monocytic cells after prolonged staining of blood films with thin dilute solutions. Dunn¹⁷ attributes a marked reaction to the hyaline cells (corresponding to the monocytes), but his microphotograph of an oxidase hyaline cell is not convincing. Evans²⁵ says that the transitionals are the only mononuclear cells that contain oxidase granules, which he²⁶ claims are in as great abundance as in the neutrophils. Naegeli²⁷ believes that the large mononuclears and transitionals give a marked reaction to the oxidase solutions. Kiyono²⁸ found a few blue oxidase granules in histiocytes, but these were inconstant and most of the histiocytes did not contain any granules. Panton and Tidy²⁹ found that only some of the hyaline cells showed oxidase granules; the proportion of the oxidase hyaline cells corresponded to the number of hyalines which showed granules according to Leishman's stain. Pappenheim³⁰ states that the monocytes do not show oxidase granules. Sapegno found oxidase granules in blood platelets, reticulated erythrocytes and megakaryocytes, but his work is still unconfirmed. 'I have not been able to find any oxidase granules in such cells in blood and bone marrow smears. To determine the cause of this difference of opinion, careful counts were made on normal blood by various methods. The results of these counts only partially substantiate the evidence that the transitionals and large mononuclears (monocytes) show oxidase granules. Some of these cells do show a few blue granules with the various staining methods. Instead of the numerous distinct blue or violaceous granules, characteristic for the neutrophils, a few scattered dark bluish or black granules were found (Pappenheim's and von Gierke's methods). The large mononuclears occasionally show a few blue granules; such mononuclears may possibly be myeloblasts. The oxidase granules of the transitionals and large mononuclears are not lipid particles. Prolonged treatment with alcohol or chloroform, however, fails to dissolve them. Rarely, fine black particles were observed in small round cells (lymphoid) as previously reported by Fiessinger and Rudowska. Graham, using his alphanaphthol pyronin method, found only a few red granules in endothelial leukocytes (transitionals and large mononuclears). These granules he believes are phagocytosed neutrophilic granules or the remains of phagocytosed leukocytes. That such cells are markedly phagocytic in character is well known. Winkler found that ptyalin, pepsin and

25. Evans, F. A.: *THE ARCHIVES INT. MED.*, 1916, **18**, 696.

26. Evans, F. A.: *THE ARCHIVES INT. MED.*, 1916, **17**, 1.

27. Naegeli, O.: *Blutkrankheiten u. Blutdiagnostic*, Leipzig, 1913.

28. Kiyono, K.: *Die vitale Karminspeicherung*, Jena, 1914, p. 53.

29. Panton, P. N., and Tidy, H. A.: *Quart. Jour. Med.*, 1914, **7**, 340.

30. Pappenheim, A.: *Ergebn. der inn. Med. u. Kinderh.*, 1912, **8**, 183.

typsin are unable to digest the granules of the leukocytes. Our results with the alphanaphthol-pyronin method (Graham) correspond with Graham's findings. Some of the large mononuclear and transitionals, however, did not show the red granules characteristic of this reaction. A few red oxidase granules, irregular in size, were found in some of the monocytes. Evans²⁶ says that the oxidase granules in the transitionals are just as numerous as in the polynuclear neutrophils. In my opinion, these cells were unquestionably metamyelocytes. The transitionals in his colored drawing resemble metamyelocytes. The myelocytes and metamyelocytes of chronic myeloid leukemias show an oxidase reaction as intensive as in the polymorphonuclear cells. Evans was dealing with premature myeloid cells.

The accompanying two blood counts (Tables 2 and 3) show the distribution of the oxidase granules in apparently normal blood.

TABLE 2.—OXIDASE GRANULES IN APPARENTLY NORMAL BLOOD

	Jenner-Giemsa* Per Cent.		Graham Per Cent.	Oxidase Stain	Pappenheim Per Cent.
Polynuclear neutrophils..	54.2				
Polynuclear eosinophils..	12.8	68.7	Many granules	66.7	Many granules
Polynuclear basophils..	0.5				
Lymphocytes	23.8	24.3	No granules	27.0	No granules
Large mononuclears	3.5	1.0	Few granules	1.3	Few granules
		1.0	No granules	0.3	No granules
Transitionals	5.2	4.0	Few granules	4.0	Few granules
		1.0	No granules	0.7	No granules

TABLE 3.—OXIDASE GRANULES IN APPARENTLY NORMAL BLOOD

	Jenner-1 Giemsa* Per Cent.		Graham Per Cent.	Oxidase Stain	Pappenheim Per Cent.
Polynuclear neutrophils..	68.0				
Polynuclear eosinophils..	6.7	72.0	Many granules	72.8	Many blue gran- ules
Polynuclear basophils....				3.0	Few blue gran- ules
Lymphocytes.....	20.3	23.0	No granules	18.4	No blue gran- ules
				0.4	Few black gran- ules
Large mononuclears.....	1.7	1.7	Few granules	0.4	Few blue gran- ules
		0.7	No granules	0.4	Few black gran- ules
Transitionals.....	3.3	2.3	Few granules	0.6	No granules
		0.3	No granules	2.2	Few black gran- ules
				1.8	No granules

* For differential blood counts I have had splendid results with Pappenheim's panoptic stain for blood smears. The method is employed as follows: (1) Jenner, three minutes; (2) dilute with distilled water 1 minute; (3) wash slide quickly and stain fifteen minutes with diluted Giemsa (20 drops to 10 c.c. of ordinary tap water); (4) wash with tap water and blot.

OXIDASE GRANULES OF PREMATURE CELLS OCCURRING IN LEUKEMIAS

The following classification of cells in the leukemias is based on the study of a large number of leukemias at the Mount Sinai Hospital (to be reported elsewhere). As the data concerning the occurrence of oxidase granules in the premature cells are very few, the oxidase reaction was carefully studied in the cells found in the various

leukemias. Schultze,^{9, 13} Marchand³¹ and Peters³² were able to identify acute myeloid leukemias by the presence of oxidase granules in ungranulated mononucleated cells, which up to that time had been considered lymphoid in character. They consider the reaction an important criterion for the differentiation of the lymphoid and myeloid leukemias. The cells which exhibit the oxidase granules were considered myeloblasts. Von Jagic,³³ Jochman and Blühdorn,³⁴ and Dunn¹⁷ found that some of the myeloblastic and promyeloblastic cells in certain myeloid leukemias failed to show oxidase granules. The presence of oxidase granules in numerous mononucleated cells is evidence of a myeloid leukemia; its absence does not indicate a lymphoid leukemia, as we shall see later.

TABLE 4.—OXIDASE REACTION IN PREMATURE CELLS. MYELOID SERIES

Type of Cell	Granules with Jenner-Giemsa	Pappenheim Oxidase	Graham
Myelocytes	Neutrophils Eosinophils Basophils	Same as polys. Same as polys. Same as polys.	Same as polys. Same as polys. Same as polys.
Myeloblasts	"Azure" or a few neutrophilic; no granules	Most of the cells show a few or more blue granules; occasionally a cell contains no granules	Few or more red granules
Myelogones.....	No granules; Auer bodies or few azure granules	No granules unless Auer bodies or azure granules are present, when these cells show the oxidase reaction limited to the granules	No granules or few red granules in cytoplasm or red Auer body
Megakaryocytes	Nuclear particles	No granules	No granules
Erythroblasts	None	No granules	No granules

We have already noted (see Table 1 of normal blood cells) the division of the white blood cells into three series; (1) myeloid; (2) lymphoid, and (3) monocytic, and the various types of cells occurring in each series. The premature and mature cells, in the various leukemias, show an absolute increase in one series, so that three main types of leukemias exist (myeloid, lymphoid and monocytic). With proper staining methods (Pappenheim's panoptic stain is especially recommended) the various types of cells are well shown and can be recognized by their staining reactions, size and granules. Premature cells also contain granules which often form the basis of the oxidase granules. The oxidase reaction of the Auer³⁵ bodies (present in myelogones) is strongly positive and appears as a distinct blue rod. A small area of neutrophilic granules at one pole of a myeloblast will manifest

31. Marchand: München. med. Wchnschr., 1911, **58**, 924 and 1215.

32. Peters, J.: München. med. Wchnschr., 1909, **56**, 1478.

33. Von Jagic, N.: Berl. klin. Wchnschr., 1910, **47**, 874.

34. Jochmann and Blühdorn: Folia haemat., 1911, **12**, 181.

35. Auer: Am. Jour. Med. Sc., 1906, **131**, 1002. Ottenberg, R.: Proc. New York Path. Soc., 1909, **9**, 1.

itself by a few blue granules at that pole. The azure granules of the myeloblasts also show a marked oxidase reaction. The reactions of the rest of the cells are shown in Tables 4 and 5:

TABLE 5.—OXIDASE REACTION IN PREMATURE BLOOD CELLS

Series	Type of Cells	Granules	Graham	Pappenheim
Lymphoid	Lymphoblasts (small and large)	Few azure	None	None
Monocytic ...	Large mononuclears and transitionals	Nuclear ticles	None	None

THE OXIDASE REACTIONS IN THE LEUKEMIAS

In view of these facts, can the oxidase reaction be considered a criterion for the differentiation between myeloid, lymphoid and monocytic leukemia? The reaction is not infallible, as the following blood count in a case of *acute myelogenous leukemia* shows.

Leukocytes, 35,800.

Differential (500 cells counted):

Myeloid Series:	Per Cent.	Absolute
Polynuclear neutrophils	5.8	2,076.4
Polynuclear eosinophils	0.2	71.6
Myelocytic neutrophils.....	3.6	1,288.8
Myeloblasts	4.8	1,718.4
Myelogones (no granules).....	73.7	26,384.6
Normoblasts	3.2	1,145.6
Lymphoid large and small lymphocytes...	8.4	3,007.2
Monocytic transitionals	0.3	107.4

It will be noticed that the myelogones (round or oval cells with reticulated, violaceous nucleus, well stained nucleolus or nucleoli and deep blue rim of cytoplasm, stained with Jenner and Giemsa stains) are the predominant cells, which can easily be confused with lymphocytes in poorly stained blood smears. The oxidase reaction (Graham's) of the same case (500 cells counted) was as follows:

	Positive, Per Cent.	Negative Per Cent.
Polynuclear neutrophils and eosinophils }	15.2	
Myelocytes		
Myeloblasts	1.4	
Lymphocytes	6.8
Myelogones	76.6
Cells showing oxidase granules.....	16.6	
Cells showing no oxidase granules.....		83.4

At the first glance, or even count, of the oxidase stain, the large number of nonoxidase cells would lead one to believe that we are dealing with a lymphatic leukemia, but the absolute increase of myelocytes, the normal number of lymphocytes, the presence of myeloblasts and the great increase of the myelogones, which is a characteristic cell of the myeloid leukemias, make the diagnosis of acute myeloid leukemia certain. A similar leukemia showing the presence of Auer bodies in the myelogones, showed a positive oxidase reaction which was confined

to the Auer granules. The absence of a positive oxidase reaction is therefore no criterion of the differentiation of the various types of leukemia. The absolute increase of a certain series of cells, ascertained from well stained blood films, is of greater importance.

The following case of *acute myeloblastic leukemia* (myeloblasts predominant) illustrates the distribution of the oxidase granules in such a leukemia.

Hemoglobin, 48 per cent.; erythrocytes, 2,336,000; leukocytes, 65,600.

Differential (500 cells counted):	Per Cent.	Absolute No.
Polynuclear neutrophils	7.0	459.2
Myelocytic neutrophils.....	9.0	590.4
Myeloblasts	55.2	36,211.2
Myelogones	20.0	13,120.0
Lymphocytes	7.2	4,723.2
Transitionals	0.4	262.4
Normoblasts	1.0	656.0
Megaloblasts	0.2	131.2

Some of the myeloblasts contain either a few premature neutrophilic granules at one pole or show scattered azure granules. A large number of the myelogones show Auer bodies and occasionally small granules.

The results with the oxidase reaction were as shown in Table 6.

TABLE 6.—RESULTS OF OXIDASE REACTION IN A CASE OF ACUTE MYELOBLASTIC LEUKEMIA

Pappenheim's oxidase method:	Per Cent.	
Polynuclears.....	6	Many blue granules
Myelocytes.....	5	Many blue granules
Lymphocytes.....	10.5	No granules
Myeloblasts and myelogones.....	78.0	Few blue granules
	0.5	No granules
Graham alphanaphthol-pyronin method:	Per Cent.	
Polynuclears.....	6.0	Many red granules
	0.5	Few red granules
Myelocytes.....	12.5	Many red granules
Lymphocytes.....	6.5	No granules
Myeloblasts and myelogones.....	72.5	Few red granules
	2.0	No red granules

In this case the myeloblasts showed a few blue granules at one pole.

The following illustrates the blood count and the oxidase reaction (Table 7) in a case with a picture of a severe anemia, leukopenia, and the presence of premature myeloid cells in the blood, especially myelogones, containing Auer bodies in a great percentage:

Hemoglobin, 35 per cent. (Kuttner); erythrocytes, 1,720,000; leukocytes, 5,800.

Differential (300 cells counted):

	Per Cent.
Polynuclear neutrophils	17.0
Polynuclear basophils	0.3
Lymphocytes	28.7
Neutrophilic myelocytes	6.3
Myeloblasts	20.7
Myelogones	26.0
Transitionals	1.0

TABLE 7.—OXIDASE REACTION IN SEVERE ANEMIA

Polynuclears and myelocytes	Per Cent. 30 4	Graham Many granules Few granules	Per Cent. 24	Pappenheim Many granules
Myeloblasts	23	Few granules	22	Few granules
Myelogones.....	10 3	Few granules (Auer bodies) No granules	11 6	Few granules (Auer bodies) No granules
Lymphocytes	30	No granules	31 2	No granules Small black granules
Transitionals.....			0.5 0.5	Few dull black granules No granules

In a *monocytic leukemia*, in which the predominant cells resembled certain large mononuclears and the transitionals of normal blood, the oxidase reaction (Table 8) was negative in all the cells except the polynuclears and myelocytes. This leukemia was similar to one described incorrectly by Klein³⁶ as a myelogonic leukemia (Case 4 of his series). The so-called myelogones of Klein were large mononuclears or degenerated forms. Some of the nuclei of the large mononuclears and transitionals were pale, and a certain amount of the nuclear substance was diffused out into the cytoplasm where it appeared as fine granules. The degenerated monocytes of this leukemia never attained the larger size of megakaryocytes, which are present in chronic myeloid leukemias. The nuclear granules did not show any oxidase reaction with a large number of methods and in spite of prolonged staining.

Monocytic Leukemia.—Hemoglobin, 68 per cent.; erythrocytes, 4,030,000; leukocytes, 245,000.

Differential (1,000 cells counted):	Per Cent.	Absolute No.
Myeloid:		
Polynuclear neutrophils	2.9	7,105
Polynuclear eosinophils	0.2	490
Polynuclear basophils	0.1	245
Myelocytes, neutrophilic	0.3	735
Myeloblasts	0.1	245
Myelogones	0.1	245
Lymphoid:		
Small lymphocytes	7.4	18,130
Large lymphocytes	0.7	1,715
Monocytes:		
Large mononuclears	67.0	164,150
Transitionals	20.4	49,980
Normoblasts	0.6	1,470
Megaloblast (one mitotic).....	0.2	490

Note: Megakaryocytoid cells (degenerating large mononuclears) are not included in this count.

TABLE 8.—PAPPENHEIM OXIDASE REACTION (500 CELLS COUNTED)

	Positive, Per Cent.	Negative, Per Cent.
Polynuclears, myelocytes and myeloblasts	4	17
Lymphocytes	79
Large mononuclears and transitionals	

36. Klein, Stanislaus: Die Myelogonie, Berlin, 1914, p. 25.

The lymphoid cells in the lymphatic leukemias do not contain oxidizing substances.

Table 9 is a summary of the oxidase reaction in the various leukemias.

TABLE 9.—THE OXIDASE REACTION IN THE LEUKEMIAS

Class	Predominating Cells	Oxidase Reaction
Myeloid.....	Myelogenic	Usually negative. Positive in a large number of cells if Auer bodies or fine granules are present
	Myeloblastic	Positive
	Myelocytic	Positive
Lymphatic.....	Lymphoblastic	Negative (a few myelocytes may be present)
	Lymphocytic (Large)	Negative
	(Small)	Negative
Monocytic.....	Transitionals and large mononuclears	Negative

THE RELATION OF THE GRANULES OF THE CELL TO THE OXIDASE REACTION

Winkler and Schultze consider the oxidase reaction to be due to the granules of the cell. In bone marrow smears one finds numerous scattered neutrophilic and eosinophilic granules, which react very distinctly with the alphanaphthol and dimethylparaphenylenediamin reagents. Panton and Tidy²⁹ found that only the transitionals and large mononuclears, which show granules with the Leishman stain, give the oxidase reaction. The granulated cells of the parotid and lachrymal glands show a marked oxidase reaction. Sapegno attributes the reaction to the ferments, which may have no relation to granules. Certain ungranulated cells, however, such as the endothelial (Ikeda²²), reticulated red cells, lymphocytes and blood platelets (Sapegno²⁴) are said to show an oxidase reaction. MacCallum³⁷ says that premature, ungranulated myeloid cells show an oxidase reaction, but this does not seem to be in conformity with the results of some of the investigators (Dunn¹⁷ and Jochmann³⁴). It is a mooted point whether one should consider the oxidation of the alphanaphthol-dimethylparaphenylenediamin to a dull black or even violaceous tinge an oxidase reaction, limited only to the myeloid cells. I have observed a distinct reaction in the reticulo-endothelial cells, and the periphery of the fat cells, in a section of a lymph node of the greater curvature of the stomach. The cytoplasm of the reticular and endothelial cells, with Pappenheim's oxidase stain, showed a dull black, diffuse coloration or fine granules; a few of these cells and most of the fat cells showed a diffuse violaceous stain. The reaction resembled that of the large mononuclears and transitionals of normal blood. The distinct blue reaction is present in myeloid cells which show neutrophilic or eosinophilic granules (mature or premature). In smears of myeloid leukemias I have found

37. MacCallum, W. G.: A Text Book of Pathology, Phila., 1916, p. 739.

that the oxidase cells correspond to the granule-bearing cells. The myelogone, the forerunner of all the myeloid cells, does not show any oxidase reaction unless Auer bodies or fine granules are present.

As a result of my investigations it may be stated that the oxidase reaction itself is not constant. Variations in results are frequently obtained in spite of careful technic, and this may account for the difference of opinion in regard to the reaction. Furthermore, the indophenol reaction is present in cells outside of the bone marrow, and large mononucleated cells which do not show the oxidase reaction are present in the bone marrow. One should therefore hesitate to attribute a myeloid origin to cells which show such a wide variation in their reaction to the oxidase stain, such as the transitionals and large mononuclears, for the origin of these cells from lymph nodes has been described by several investigators, notably by Weidenreich and Downey.³⁸ Furthermore, the value of the oxidase reaction is still further lessened by the fact that certain cells of definite myeloid origin, such as the myelogones and certain myeloblasts, do not show the oxidase reaction.

CONCLUSIONS

1. The oxidase reaction is not conclusive evidence of the myeloid origin of blood cells.
2. The reaction is not present in ungranulated premature bone marrow cells.
3. The reaction in premature bone marrow cells depends on the presence of granules (neutrophilic and so-called azure granules and Auer bodies).
4. The reaction in transitionals and large mononuclears is never as intense as in myeloblasts or neutrophilic myelocytes and often of a somewhat different character. The reaction may be absent in transitionals and large mononuclears, but some large mononuclears of normal blood show a reaction similar to myeloblasts.
5. The reaction is not present in lymphocytes, red blood cells, blood platelets, megakaryocytes and plasma cells (Türk's irritation form) of normal and leukemic blood.
6. Morphology, with good polychromatic staining of the blood cells, is of greater importance in the identification of the leukemias than the oxidase reaction.

1 East One Hundredth Street.

38. Weidenreich and Downey: *Arch. f. mikr. Anat.*, 1912, **80**, 306.

RELATION OF PELLAGRA TO LOCATION OF DOMICILE IN SPARTAN MILLS, S. C., AND THE ADJACENT DISTRICT *

J. F. SILER, M.D.

Major, Medical Corps, U. S. Army

P. E. GARRISON, M.D.

Passed Asst. Surg., U. S. Navy

AND

W. J. MACNEAL, M.D.

NEW YORK

INTRODUCTION

The geographic distribution of pellagra has always been a remarkable feature of this disease and has frequently been discussed by various investigators since the earliest recognition of pellagra. Special significance has usually been ascribed to this peculiar geographic distribution. Thus, for example, it has been argued that people who live in the same region consume the same diet and so are subject to the same dietary deficiencies, or again, that people living in certain regions are exposed to the attacks of certain insects, which live there, and thus acquire a disease transmitted by these insects. The possibility of such discordant interpretations indicates that a mere superficial examination of the geographic distribution of pellagra will not suffice to solve its etiology. An examination of this striking feature of the disease is nevertheless of obvious importance and the possibility still remains that a more intimate and exact study of geographic distribution may contribute much to our knowledge of pellagra. Such a study we hope to present in a series of papers on this general subject, beginning with a consideration of small geographic units and subsequently proceeding to a discussion of larger areas.

A first attempt at an intimate and exact study of geographic distribution of pellagra in small unit areas was made in our paper on the

* Submitted for publication March 22, 1917.

* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* This is the tenth paper in the series now appearing in THE ARCHIVES, constituting the third report of the Robert M. Thompson Pellagra Commission. The epidemiologic surveys in 1915 and 1916, utilized in this paper, have been made and the final copy of the paper itself has been written since Dr. Garrison and Dr. Siler were recalled to active service in the Medical Corps, U. S. Navy, and the Medical Corps, U. S. Army, respectively. They are, therefore, not personally responsible for the observations of the last two years, for the compilation of the data, or for the deductions drawn from them.

relation of pellagra to domicile, presented before Section K of the American Association for the Advancement of Science at the Atlanta Meeting, January 2, 1914, published in our second progress report.¹

A further paper dealing in part with the same topic was presented at the Third Triennial Pellagra Conference at Columbia, S. C., in October, 1915, and an extended abstract of it is to appear in the proceedings of that conference when published. As a result of these studies we concluded that pellagra spread from preëxisting cases and was transmitted through only relatively short distances in the communities studied. The data upon which the discussion and conclusions were based were presented only in summarized form and probably, in part at least, because of this fact, the evidence seems not to have been fully and clearly appreciated.

On this account, we have decided to present in some detail our material relating to geographic distribution of pellagra, so that those who care to examine the material may be able to decide for themselves whether our analysis of the data is or is not fallacious.

In the present paper the community of Spartan Mills, Spartanburg, S. C., and the immediately adjacent district will be considered, with particular attention to the exact residence of each pellagrin in this community and the possible relation between location of domicile and the origin of new cases of pellagra.

GENERAL DESCRIPTION OF THE COMMUNITY *

The community of Spartan Mills is situated in the fifth and sixth wards in the northwestern part of the city of Spartanburg. When the first mill was erected its capacity was 30,000 spindles. Several years later a second mill was constructed and in 1914 the capacity of the two mills was 85,000 spindles. The motive power is steam and the manufactured products are sheetings, shirtings and narrow print cloth. Most of the village is situated on high ground with excellent drainage. Water for the mills is impounded in an open reservoir just north of the mills. The village is laid out in streets and in addition to the tenement houses, has several stores, a social settlement house (the Wesley Home at 339 Brawley Street), two churches and a hospital, located at 328 Forest Street. This building was used as a general hospital until

1. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: A Statistical Study of the Relation of Pellagra to Use of Certain Foods and to Location of Domicile in Six Selected Industrial Communities. *THE ARCHIVES INT. MED.*, 1914, **14**, 292; Second Progress Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate Medical School and Hospital, New York, 1915, p. 15.

* We are indebted to Mr. W. S. Montgomery, President of Spartan Mills, and to Mr. W. J. Britton, Superintendent of Spartan Mills, for important information used in this section of the paper.

1913, in which year it was converted into a charity pellagra hospital under our supervision. In 1914 the building was placed in charge of the U. S. Public Health Service and after extensive changes it was reopened as a pellagra hospital in the fall of that year. Each tenement is allotted a plot of ground for garden and the tenants are permitted to keep cows on their premises. Nearly all the children under 12 years attend the public schools of the city, although this was not the case several years ago.

The expansion of the city of Spartanburg during the past twenty years has occurred in part in this district, so that new streets lined with private dwellings have appeared in the district about the mill



Fig. 1.—Spartan Mills, looking northeast from the corner of Forest and College Streets. The houses are examples of the larger dwellings constructed since 1907.

village proper in the last ten years and new houses have been erected here very recently.

When first constructed, the village contained 155 tenement houses located on Jennings, Burnett and Colton Streets and in the region east of the present Brawley Street. The original houses on Jennings, Burnett and Colton Streets are still used but the rest of the village was swept away by a great fire in 1907. This portion was rebuilt and the village was extended westward, so that at present there are 265 tenement houses, some of them accommodating two or more families. All the houses are of wood with open brick foundation. Most of them contain four, five or six rooms, but a few contain ten rooms. The old original houses, indicated by oblong rectangles on the map, are two-

storied, four-room structures, built at an average cost of \$110 per room. The newer houses are of much better construction. Figure 1 shows a view of College Street, looking northeast from the corner of Forest and College Streets. Figure 2 was photographed from the second story of the hospital at 328 Forest Street, looking west. The bridge at the upper left corner of this picture is at the point where Farley Avenue crosses the railroad track.

The assignment of houses depends on the character and the reliability of the operatives and no family is permitted to occupy a house unless some of its members are employees of the company. The houses on Jennings and Burnett Streets are rent-free and those on Colton

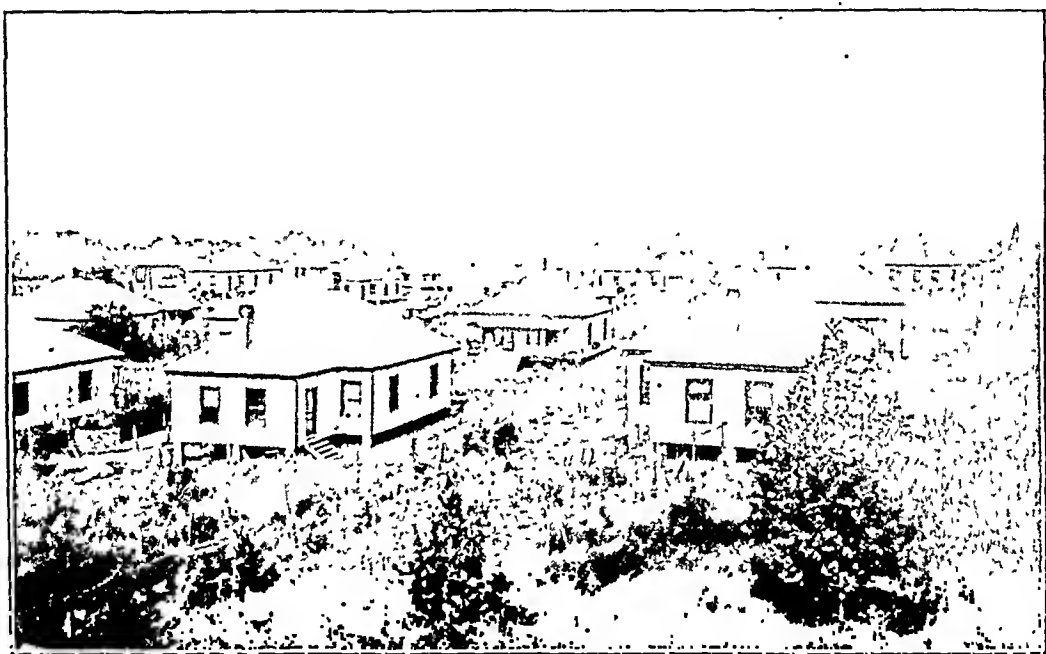


Fig. 2.—Spartan Mills, looking west from the back of the second floor of the hospital building at 328 Forest Street. This picture shows the type of smaller houses constructed since 1907.

Street rent for 25 cents per room per month. For the remaining houses the rental varies from 40 cents to \$1.00 per room per month, the average being about 60 cents. Until 1893 no rents were charged. The present rents suffice for repairs and maintenance.

The water supply for the community was obtained from open wells until 1910. Since then the supply has been furnished from pipes connected to the water mains of the city of Spartanburg, hydrants being located at convenient intervals along the streets. Late in 1913 these pipes were continued into each house, the installations being completed in May, 1914. The water used since 1910 has been, therefore, the same as for the city as a whole.

The method of disposal of human excreta until 1905 was by means of open surface privies, the excreta being deposited on the surface of the ground. In 1905 wooden boxes were installed underneath the seats. Ultimate disposal was by scavenger service, the annual cost being \$400 for the entire village. The boxes were emptied once a week. No attempt was made to screen against flies; the doors of the outhouses were left open, seats uncovered and the catch-boxes were not water tight. In 1913 the installation of a water-carriage system of sewage disposal was begun and this was completed in May, 1914. The time when each group of houses was connected with the sewer is indicated on the maps for 1913 and 1914, Figures 9 and 10. The total water closets installed numbered 316. The total cost of the installation of piped water, kitchen sinks and water closets was approximately \$39,000. The water is now purchased from the city at the flat rate of \$2,460 per year and the estimated cost of inspection and maintenance is \$600 per year. Each tenant is required to pay an extra rental of \$1.00 per month for the sanitary improvements and the annual income on this account is approximately \$3,500. With very rare exceptions, the householders are highly pleased with the improvement and gladly pay the extra charge.

During the period of our survey, 1912 to 1916, inclusive, there was observed a marked improvement in general sanitation in this community. Most notable, of course, was the sewer installation. Along with that there has been also improvement in general cleanliness, with diminished scattering of garbage and refuse. In 1913 and 1914 there was a very noticeable increase in the use of wire screens on windows and doors, but in 1915 and 1916 these had generally become dilapidated and had not been renewed, partly because flies were much less troublesome than in previous years.

INSECTS

The house fly (*Musca domestica*) is very abundant during the summer but considerably less numerous since the improvement in sanitation in 1914. The stable fly (*Stomoxys calcitrans*) is moderately abundant. The custom of keeping cows in the immediate vicinity of the dwellings has been continued in this community and this fly was apparently as abundant as ever in 1916. Mosquitos are not numerous although some are observed at times. The bedbug (*Cimex lectularius*) is present in nearly every house, but its numbers vary according to the housekeeper. The head louse (*Pediculus capitis*) is common, particularly on the children. The body louse (*Pediculus vestimenti*) has not been observed. The sand-fly (*Simulium*) has not been observed in this village, although potential breeding places exist there. In 1916 large numbers of small, black flies were observed. These appeared not

to be blood-sucking flies, but were seen especially on the margins of the eyelids of the children, many of whom had a mild conjunctivitis. During our survey in August, 1916, these flies were a frequent personal pest, always attacking the eyes. Apparently they are very common on cattle.

POPULATION

The population of this community has come, for the most part, from the mountainous section of western North Carolina, with a few

TABLE 1.—DISTRIBUTION OF THE WHITE POPULATION OF SPARTAN MILLS
ACCORDING TO SEX AND AGE, IN EACH YEAR

Age	1913			1914			1915			1916		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
0-4	83	98	181	95	102	197	101	88	189	103	109	212
5-9	89	103	192	85	102	187	81	108	192	94	105	199
10-14	102	101	203	96	110	206	92	95	187	95	93	188
15-19	97	99	196	86	95	181	109	100	209	118	107	225
20-24	82	72	154	94	75	169	101	70	174	114	74	188
25-29	70	54	124	58	48	106	52	41	96	55	57	112
30-34	46	47	93	57	43	100	45	36	81	47	33	80
35-39	43	33	76	48	39	87	63	46	109	51	48	99
40-44	43	31	74	41	30	71	47	33	80	49	32	81
45-49	19	22	41	18	23	41	23	27	50	29	30	59
50-54	21	23	47	24	15	39	18	22	40	19	18	37
55-59	13	14	27	14	11	25	18	13	31	20	21	41
60-64	8	12	20	17	15	32	14	10	24	12	7	19
65-69	5	7	12	5	7	12	5	6	11	3	5	8
70-74	7	6	13	6	8	14	5	6	11	6	5	11
75-79	3	1	4	2	0	2	4	2	6	6	3	9
Over 80	0	1	1	0	1	1	1	2	3	1	1	2
Age unknown	8	9	22*	8	9	20†	2	3	5	0	0	0
Total	742	733	1,480*	754	733	1,490†	787	711	1,498	822	748	1,570

* Including five individuals whose sex and age were not recorded.

† Including three children whose sex and age were not recorded.

families from eastern Tennessee. The supply of labor from the immediate vicinity is irregular and depends very much on the condition of the farm crops. In a poor year many come from the farms into the cotton mill. Foreign labor was not employed. A census of the population taken by us in 1913, 1914, 1915 and 1916 yielded the statistics shown in Tables 1, 2 and 3. The average size of families was about four members. Up to 1914 approximately 25 per cent. of the

TABLE 2.—DISTRIBUTION OF THE WHITE POPULATION OF DISTRICT ADJACENT TO SPARTAN MILLS, ACCORDING TO SEX AND AGE, IN EACH YEAR

Age	1913			1914			1915			1916		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
0-4	7	4	11	13	20	33	19	20	39	20	26	46
5-9	6	7	13	20	15	35	22	13	35	19	13	32
10-14	8	11	19	11	15	26	12	16	28	16	12	28
15-19	3	4	7	11	7	18	15	4	19	14	12	26
20-24	5	2	7	14	7	21	15	8	23	16	9	25
25-29	6	6	12	13	16	29	15	15	30	16	13	29
30-34	4	2	6	10	7	17	9	10	19	9	14	23
35-39	3	6	9	6	6	12	10	10	20	15	8	23
40-44	1	0	1	3	5	8	5	4	9	5	4	9
45-49	2	2	4	5	2	7	5	3	8	7	6	13
50-54	1	3	4	3	4	7	4	3	7	7	5	12
55-59	0	0	0	2	3	5	2	3	5	3	4	7
60-64	2	0	2	5	2	7	6	3	9	2	2	4
65-69	1	1	2	3	2	5	3	2	5	7	2	9
70-74	0	0	0	0	0	0	0	1	1	0	1	1
75-79	1	0	1	1	0	1	0	0	0	0	0	0
Over 80	0	0	0	0	0	0	0	0	0	0	0	0
Age unknown	1	1	2	1	1	2	0	0	0	2	7	9
Total	51	49	100	121	112	233	142	115	257	158	138	296

TABLE 3.—DISTRIBUTION OF NEGRO POPULATION IN SPARTAN MILLS AND IN ADJACENT DISTRICT, ACCORDING TO SEX AND AGE, IN EACH YEAR

Age	1913			1914			1915			1916		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
0-4	3	0	3	5	0	5	5	1	6	3	0	3
5-9	2	0	2	2	1	3	2	0	2	2	0	2
10-14	1	3	4	1	3	4	1	2	3	1	1	2
15-19	0	4	4	0	4	4	0	5	5	0	4	4
20-24	2	1	3	4	2	6	3	1	4	3	2	5
25-29	1	0	1	3	0	3	5	2	7	4	2	6
30-34	0	1	1	0	1	1	0	2	2	1	1	2
35-39	1	1	2	2	1	3	1	0	1	1	1	2
40-44	0	0	0	0	1	1	0	1	1	0	0	0
45-49	1	1	2	1	1	2	1	0	1	1	1	2
50-54	0	1	1	0	1	1	0	2	2	0	1	1
55-59	0	0	0	0	0	0	0	0	0	0	1	1
60-64	0	0	0	0	0	0	1	0	1	1	0	1
65-69	0	0	0	0	0	0	0	0	0	0	0	0
70-74	0	0	0	0	0	0	0	0	0	0	0	0
75-79	0	0	0	0	0	0	0	0	0	0	0	0
Over 80	0	0	0	0	0	0	0	0	0	0	0	0
Age unknown	0	0	0	0	0	0	0	0	0	0	0	0
Total	11	12	23	18	15	33	19	16	35	17	14	31

population remained less than a year. Since 1914, however, there has been a greater tendency for the people to remain.

The negro residents, as shown in Table 3, formed a very small proportion of the population in this particular community. A few were employed in the mill, while some of the women were cooks or laundresses for the white residents. In the more well-to-do families in the adjacent district, negro women were commonly employed by the day as maids. These, however, have not been included in Table 3, as

TABLE 4.—DISTRIBUTION OF THE WHITE MILL OPERATIVES RESIDING IN SPARTAN MILLS PROPER, ACCORDING TO SEX AND AGE, IN EACH YEAR

Age	1913			1914			1915			1916		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
Under 12	2	1	3	1	2	3	1	1	2	0	1	1
12-14	55	55	110	48	59	107	49	47	96	39	43	82
15-19	87*	91	178	68	77	145	92	91	183	90	98	187
20-24	50	52	102	60	61	121	76	62	138	67	60	127
25-29	25	39	64	26	37	63	29	34	63	29	51	80
30-34	6	42	48	19	36	55	17	26	43	15	25	40
35-39	7	27	34	11	36	47	10	37	46	12	42	54
40-44	6	21	27	8	20	28	11	19	30	15	25	40
45-49	3	16	19	1	16	17	4	20	24	4	20	24
50-54	1	15	16	0	10	10	0	15	15	0	16	16
55-59	0	11	11	0	10	10	1	12	13	1	14	15
60-64	0	7	7	1	10	11	1	5	6	0	4	4
65-69	1	5	6	0	2	2	0	3	3	0	4	4
70-74	0	1	1	0	3	3	0	1	1	0	1	1
75-79	0	0	0	0	0	0	0	1	1	0	1	1
Over 80	0	0	0	0	0	0	0	0	0	0	0	0
Age unknown	5	9	14	1	4	5	0	1	1	0	0	0
Total	248	392	640	244	353	627	300	375	675	281	403	686

they returned at night to their homes which were in the negro quarter of the city of Spartanburg, beyond the limits of the mill village.

INDUSTRIAL AND ECONOMIC CONDITIONS

When families coming from the mountains, having only unskilled laborers, apply for work in the mill, the authorities require that they have at least three potential operatives in order to be assigned a house. In the case of skilled laborers this requirement is lowered, and some families are accepted with only one operative on the pay-roll. Families unable to meet these requirements have been compelled to obtain houses

beyond the confines of the mill village proper. On Aug. 14, 1914, there were 849 employees, 809 white and 40 colored. Of the white employees, 630 * lived in the mill village and 179 outside of it.

The distribution, according to sex and age, of the mill operatives residing in the mill village in each of the four years, 1913 to 1916, inclusive, is indicated in Table 4. Some residents of the adjacent district were also employed by the mill company, but in most instances these persons held positions of responsibility and of higher remuneration. These have not been tabulated.

In this mill we were able to obtain, through the kindness of Mr. W. J. Britton, Superintendent of the mill, explicit information in

TABLE 5.—DATA IN REGARD TO LABOR IN THE SPINNING ROOM OF SPARTAN MILL NO. 2

Group	March 22, 1904			Feb. 15, 1911		
	Spinners	Sides Attended	Total Sides for the Group	Spinners	Sides Attended	Total Sides for the Group
1	2	1	2	0	1	0
2	10	2	20	1	2	2
3	10	3	30	0	3	0
4	14	4	56	5	4	20
5	9	5	45	0	5	0
6	38	6	228	9	6	54
7	1	7	7	0	7	0
8	0	8	0	28	8	224
9	0	9	0	1	9	9
10	0	10	0	8	10	80
11	0	11	0	1	11	11
12	0	12	0	4	12	48
Total	84	4.62	388	57	7.86	448

regard to wages actually paid to a group of operatives in one of the spinning rooms in March, 1904, in February, 1911, and in September, 1914. This is the only instance in which we have been able to obtain accurate figures for periods of time widely separated. On March 22, 1904, the superintendent recorded the actual work performed and the wages in the spinning-room of Mill No. 2 and again on Feb. 15, 1911, he made a similar record for the same room. The figures for work performed are shown in Table 5.

* Table 4 shows 627 white employees living in the village proper. This table presents the data obtained by our census in June and July, 1914. The figure 630 was obtained from the mill records for the day, Aug. 14, 1914.

In 1904 the rate of pay was 8 cents per side, so that the average daily wage of the eighty-four employees in this room was 37 cents. In 1911 the rate was 11 cents per side, so that the average wage of the fifty-seven employees was 86 cents per day. In September, 1914, the average number of sides per spinner in this room was found to be nine and the rate of pay was still 11 cents per side, with an increase to 11½ cents for those who worked full time. The average daily wage in 1914 was, therefore, 99 cents. This alteration in wages seems, according to available information, to be typical of the economic changes in the cotton-mill industry in the South during this time. There has been a considerable increase in wages in ratio to the amount of work performed, amounting to approximately 40 per cent. since 1904, but much more important than this has been the increase due to the improved efficiency of the individual worker, brought about through education and the installation of refined machinery. Thus, in 1911 only 57 spinners accomplished more work than the 84 employed in the same room in 1904. It may be mentioned, also, that the number of working hours per day was eleven in 1904 and ten in 1914. Many of the employees of the spinning room were children between 12 and 16 years of age.

In 1914 the adult mill workers were paid about \$1.20 per day, the men receiving a little more than the women, on an average. The number of wage earners per family was variable, the average being about two and a half. The average monthly wage per family was between \$65 and \$75. From 1904 to 1914 it is estimated that the average cash wage of mill operatives had increased 50 per cent. About 10 per cent. of the operatives saved a part of their wages. Some owned property near the mill village and a few had money on deposit with the treasurer of the mill, on which interest was allowed at the rate of 6 per cent. In 1914 the number of employees with money on deposit was somewhat less than in previous years.

In 1915 economic conditions in the mill village were less favorable than in 1914. There was a considerable influx of workers from the surrounding district and the less skilled operatives were unable to work full time. The business depression, however, affected the mill people less than the farmers, because the mills continued to run and to pay the same scale of wages. In 1916 economic conditions improved considerably, the excess of hands found work elsewhere and there was a slight increase in the scale of wages paid.

GENERAL DIETARY

The general dietary of the people in the village was investigated by personal interview at the house of every family in it, by interviews with

the mill authorities and with the managers of the stores and meat markets located in and near the village. A comparative study of the relation of the use of particular foods to pellagra, published in our second report,¹ included data obtained in this village, there designated as Village Sp. Since the publication of that paper the interest in the relation of diet to pellagra seems to have shifted from the question of a single particular food to a consideration of general nutritional sufficiency of the diet or to the possible absence of some hypothetical essential element from the diet. In a later paper we hope to contribute something to the discussion of this somewhat intangible conception; in the present instance, only the recorded information in regard to general dietary will be stated.

As the village is located within the city of Spartanburg many purchases are made from stores and markets having no connection with the mill company. About half the families made the bulk of their purchases at the Company Store. There were two meat markets within the community, one on Green Street and one on Howard Street, and a third just at the edge of it on Wofford Street. The owner of the market on Green Street had conducted this shop since 1907. During the summer he sold one carcass of beef per week and in winter two beeves per week and considerable fresh pork. Fresh beef sold for 10 cents per pound in 1907 and for 20 cents per pound in 1914, and he thought that less of it was used in 1914 than in previous years. The butcher on Howard Street had kept a meat shop in or near the village for twenty years. He said that the mill people ate less fresh meat than the people of the surrounding neighborhood, both classes being among his patrons. Much less fresh meat was used during the summer. Fresh pork was used extensively during the winter, especially by the mill people. From April to October he handled two beeves per week, and from October to April between four and five beeves per week. He received 10 cents per pound for beef in 1904 and 20 cents in 1914.

About one quarter of the families in the mill village possessed one or more cows and many other families purchased milk daily. Hogs were not allowed within the city limits. Chickens were kept by many families and eggs were quite generally used, more especially, of course, in April, May and June.

Each householder had a garden plot and approximately 90 per cent. raised a garden every year, the common vegetables being corn, snap beans, peas, tomatoes, onions, okra, butter beans, cabbage and turnips. Fresh vegetables were also sold by peddlers and by the stores. The gardens in 1914 were the poorest in many years. They were somewhat better in 1915, but again rather poor in 1916.

The staple articles of diet used throughout the year were wheat flour, cornmeal, bacon, canned vegetables, butter-milk, butter and, to a less extent, eggs. During the summer the staple vegetables were green corn, snap beans, okra, onions, butter beans, cabbage, tomatoes and peas. During the winter the staple vegetables were white potatoes, sweet potatoes (yams), army beans, navy beans, field peas and canned vegetables. Fresh beef was quite generally used in winter, but much less in summer. Fresh pork was extensively used during the winter. In 1913 our house-to-house inquiry indicated that more fresh meat was eaten in this mill village than in any other in Spartanburg County. We could not discover any marked changes in dietary habits during the past ten years which would serve to explain the absence of pellagra from the village from 1900 to 1905 and its high rate of prevalence from 1911 to 1914. Furthermore a careful inquiry during our house-to-house canvass in 1915 and 1916 failed to reveal any general change in the dietary habits of this population from those of previous years.

PREVAILING DISEASES

The acute infectious diseases of childhood occasionally prevailed here in epidemic form. Diarrheas and dysenteries were very prevalent among both children and adults, especially during the summer months, up to 1914. Since then there has been a remarkable improvement in this respect. The typhoid rate was always disproportionately high in this part of the city until 1914, since which time only very few cases of this disease have occurred here. Pulmonary tuberculosis was always present, with one or two deaths from it each year. In 1916 there were two deaths from consumption. Indigenous malaria did not occur and hookworm disease was only occasionally observed.

PELLAGRA IN THE SPARTAN MILL DISTRICT PREVIOUS TO 1912

The earlier history of pellagra in this village is somewhat obscure. So far as we have been able to ascertain, pellagra was not present before 1905. In 1905 and 1906 Pellagrin 633 lived in a house located on Forest Street, where House 338 now stands. The old house was destroyed in the great fire of 1907. This man, Pellagrin 633, did not suffer recurrence of pellagra in 1905 or 1906.

In 1907 a woman, Pellagrin 361, moved into a house on Colton Street, probably 131 Colton Street, although it may have been 127 or 135. She is known to have had pellagra there in 1907, but whether she had previously suffered from it is uncertain. Another woman, Pellagrin 445, who was socially intimate with her, also had pellagra in 1907 at 254 College Street. The record in regard to her is not quite clear either. It is possible that her first attack occurred in 1906 at

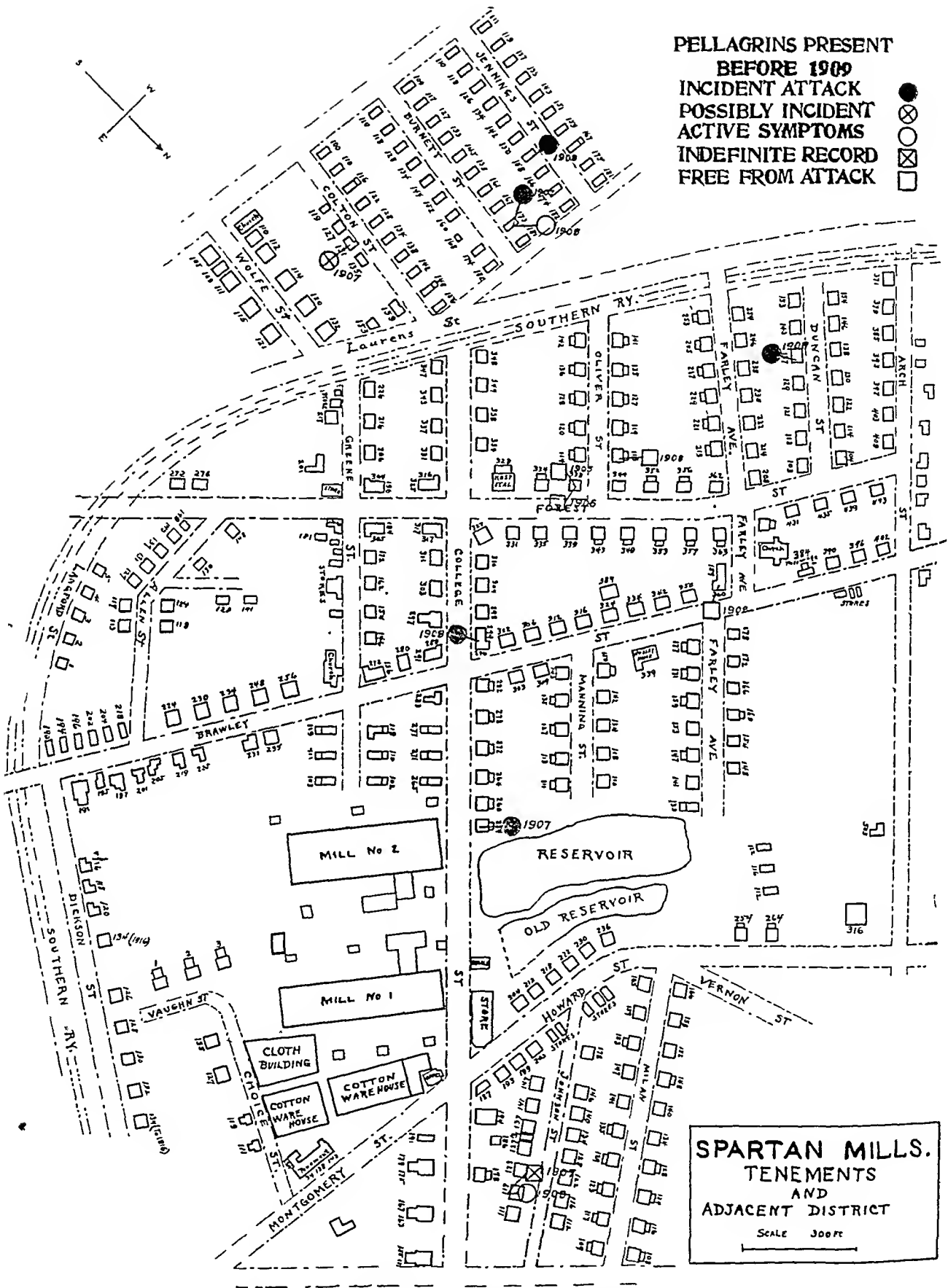


Fig. 3.—Map of Spartan Mills and the district adjacent to it, showing the location and character of all known cases of pellagra present previous to 1909.

226 Green Street, but the weight of evidence indicates that the initial attack appeared at 254 College Street. At 175 Burnett Street Pellagrin 444, a girl aged 3, developed pellagra in 1907, shortly after moving there. At 117 Johnson Street, a house outside the mill property, Pellagrin 778 resided in 1907 and 1908. She appears to have suffered her initial attack in 1906. Whether she had a recurrence in 1907 is uncertain.

In 1908 Pellagrin 444 suffered a recurrence at 175 Burnett Street and Pellagrin 778 had a recurrent attack at 117 Johnson Street. Three possibly incident cases appeared. Pellagrin 1229, a married woman, had pellagra at 296 Brawley Street. There is no record of the length of her residence there, nor do we know whether or not she had pellagra before. At 158 Jennings Street Pellagrin 1441, a married woman, aged 37, developed an initial attack in 1908. She had lived in this house since 1905. In 1909 she suffered a recurrence in North Carolina and died there on May 17, 1909. The third incident case was that of Pellagrin 364, a girl aged 7, who suffered her initial attack at 137 Duncan Street and who died of pellagra in this same house in July, 1909. The family came from North Carolina, but the length of their residence in Spartan Mills or in the house at 137 Duncan Street is unknown. In 1908 there were two pellagrins without recurrence in the community. One of these, Pellagrin 633, lived at 189 Farley Avenue. This was the same man who had lived at 338 Forest Street in 1905 and 1906 without recurrence. The other patient, Pellagrin 70, lived at 113 Oliver Street from April in this year. She had been a pellagrin since 1905.

In 1909 Pellagrin 444 suffered a recurrence at 175 Burnett Street, the same house in which she had an initial attack the previous year. Pellagrin 364 had a recurrence and died at 137 Duncan Street. At 135 Milan Street Pellagrin 296, a woman who had suffered from the disease since about 1903, moved in about January 1, 1909, and died of pellagra in June, 1909. An unrelated woman, Pellagrin 115, lived in this same house, or in a house next door, from February to July, 1909, and she suffered a first attack of pellagra here in June, 1909. In July, 1909, she moved to 133 Farley Avenue, where her residence is indicated by a hollow circle. At 137 Johnson Street Pellagrin 116, a widow, had been living with her son since October 4, 1907. She suffered a first attack of pellagra in the spring of 1909. She associated with Pellagrin 296, who died at 135 Milan Street that year, but we have not been able to learn the details in regard to this association. At 177 Farley Avenue Pellagrin 372, a man who had resided there since 1907, suffered a definite attack of pellagra in 1909. There is some evidence that he had had pellagra the preceding year, but it is not very definite. At 150 Manning Street a married woman, Pellagrin 365, died of pel-

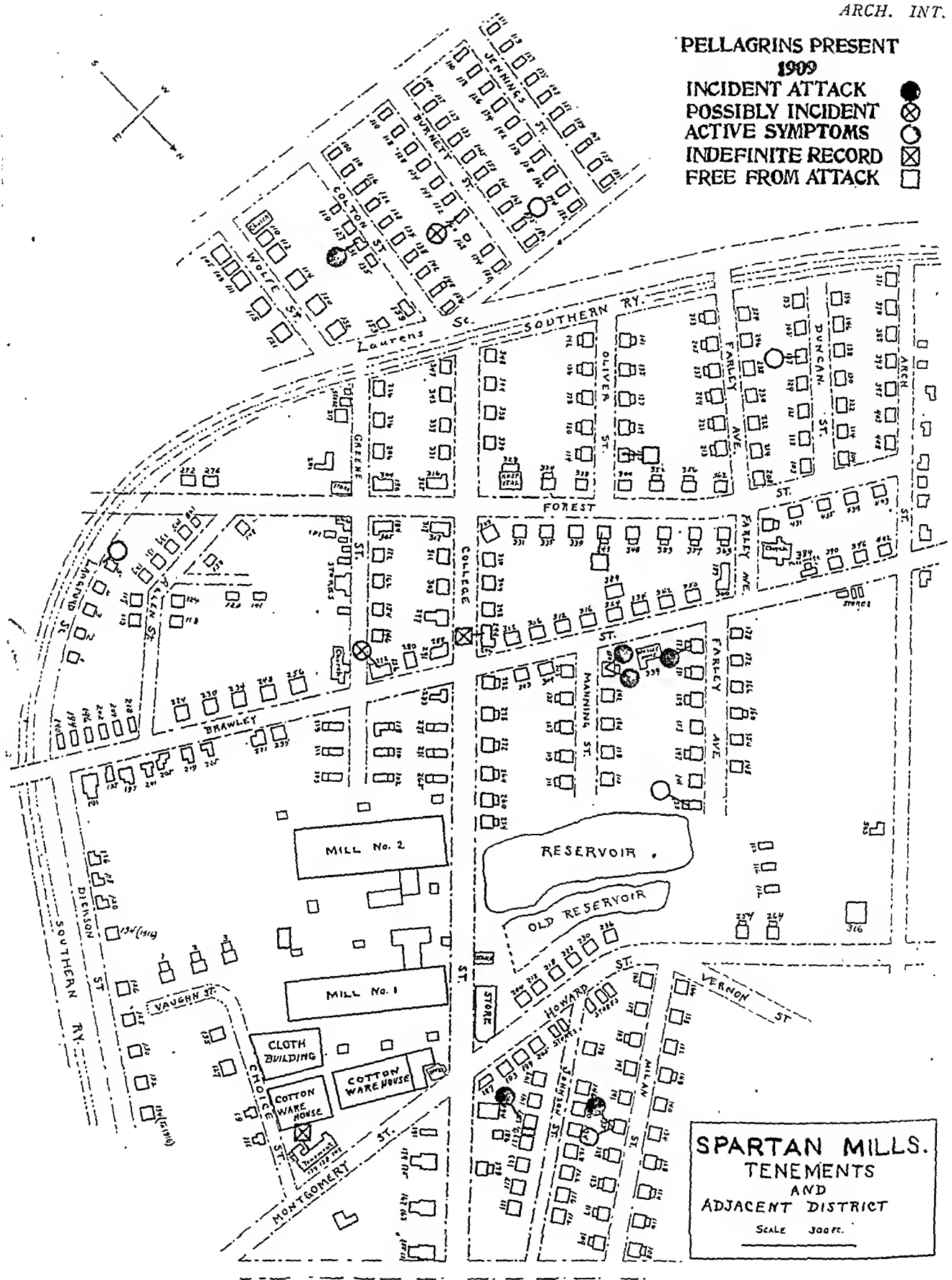


Fig. 4.—Map of Spartan Mills and the district adjacent to it, showing the location and character of all known cases of pellagra present in 1909.

lagra on June 2, 1909, and her husband, Pellagrin 1275, had an attack of the disease at the same time. After her death he went to the mountains in North Carolina and is said to have recovered. Further information is lacking and we do not know whether one or both of these persons may have had pellagra in a previous year, nor do we know how long they had resided in this house. The sixth incident case placed in this community in 1909 was that of Pellagrin 237 at 131 Colton Street. The first erythema in this case occurred in the spring of that year. From 1902 to 1908 she had resided at 114 Wolfe Street, immediately in the rear of 131 Colton Street. A case possibly incident in Spartan Mills in 1909 was that of Pellagrin 94 at 272 Brawley Street. This patient was a woman who moved here in March, 1909,

TABLE 6.—ACTIVE CASES OF PELLAGRA IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1910, BUT NOT INCIDENT HERE IN 1910

House	Residence Period	Pellagrin	Sex	Age
117 Allen.....	February on.....	445*	F	25
175 Burnett.....	To June.....	444*	F	6
116 Colton.....	June on.....	444*	F	6
131 Colton.....	Entire year.....	237	F	56
132 Dickson.....	Summer on.....	515	M	53
133 Farley.....	Entire year.....	115	F	26
177 Farley.....	Entire year.....	372	M	49
137 Johnson.....	Entire year.....	116	F	50
5 Langford.....	To February.....	445*	F	25
138 Montgomery.....	To February.....	22	M	7

* This case appears twice in this table because of change of residence during the year. It should be mentioned, also, that Pellagrins 64 and 65, in whose cases the initial erythematata appeared at 160 Burnett Street in 1910, moved to 371 Arch Street in October, 1910, and are indicated there by hollow circles on the map for 1910, Figure 5.

and developed an initial erythema in April, 1909. Pellagrin 64 was a second patient in whose case the disease was possibly incident in 1909 at 160 Burnett Street. His erythema appeared in February, 1910, in the same house where he had lived since 1907. In the apartment house at 138 Montgomery Street Pellagrin 22, a boy aged 6, resided from February, 1909, until February, 1910. He had his first attack in 1908, before moving here, but whether the disease recurred in 1909 is uncertain. It did recur in 1910, however. At 5 Langford Street Pellagrin 445 lived during 1909 and she suffered a recurrence there. One old pellagrin, without recurrence, resided in the village in 1909, namely, Pellagrin 70, who lived at 113 Oliver Street until September and thereafter at 343 Forest Street. This patient is indicated by hollow circles

on the map (Figure 4) at both of these residences. The record of Pellagrin 1229 at 296 Brawley was indefinite in 1909.

In 1910 there was only one pellagrin without recurrence living in this community, namely, Pellagrin 200 at 288 Brawley Street from January to July, 1910. There were two for whom the record of recurrence is indefinite: Pellagrin 1229 at 296 Brawley Street and Pellagrin 70 who lived at 343 Forest Street until March and at 334 Forest Street for the rest of the year. There were eight pellagrins in whom the disease was active in 1910, whose initial attack occurred previous to 1910 or at some other place in 1910. These cases are shown in Table 6. Two of these, Pellagrins 444 and 445, changed their residences in 1910 from 175 Burnett Street and 5 Langford Street to 116 Colton Street and 117 Allen Street, respectively. They are indicated at each of their residences by hollow circles on the map for 1910, Figure 5.

There were six cases of pellagra in which the initial attack in 1910 possibly, but not definitely, occurred in this district in 1910. At 397 Arch Street Pellagrin 198 resided from December, 1910, to January, 1911. In this case the initial erythema appeared in March, 1911, after he had removed to 343 College Street. Previous to December, 1910, he had lived at 3 F Street, Inman Mills, next door to Pellagrin 37. He has been considered as possibly incident at each of these three domiciles. As he was a man 40 years of age, the probable origin would appear to be at Inman, with an incubation period of at least five months. At 160 Burnett Street Pellagrin 64, a man aged 54, resided from 1907 to October, 1910, and in this case the initial erythema appeared in February, 1910. He is considered to have contracted the disease at this house, but probably incident in 1909 rather than in 1910. At 142 Colton Street Pellagrin 374, a boy aged 8, resided from March to the end of 1910 and developed an initial erythema in April. Previously he had lived at Saxon Mills. At 137 Johnson Street Pellagrin 53, a woman aged 42, lived with and nursed her mother, Pellagrin 116, during attacks of pellagra in the spring of 1909 and the spring of 1910. In the summer of 1910 she, herself, developed an initial erythema at her home at Pacolet Mills. At 113 Oliver Street Pellagrin 834, a woman aged 46, visited in 1910. She suffered an attack of pellagra some time after her arrival in March and she died of pellagra on September 9, 1910, in the Good Samaritan Hospital at 328 Forest Street. It is not improbable that she had pellagra before coming to this community, but her case is considered as possibly incident here. At 120 Wolfe Street Pellagrin 91 was living from November, 1909 to August, 1910. She was ill at this house with sore mouth, diarrhea and loss of weight. Erythema was not observed in this year, but did appear in 1911. She may have had pellagra in 1910.



Fig. 5.—Map of Spartan Mills and the district adjacent to it, showing the location and character of all known cases of pellagra present in 1910.

Of these six rather problematical cases, three probably contracted pellagra elsewhere, or in a preceding year, namely, Pellagrins 198, 374 and 834; while three, namely, Pellagrins 64, 53 and 91, in all probability contracted the disease in this community.

The eleven cases of pellagra which have been designated as incident in this community in 1910 are shown in Table 7 and the house in which each case had its origin is indicated by a red circle on the map, Figure 5. Of the eleven cases, seven originated in houses in which antecedent pellagrins were living. Two cases arose in houses situated next door to active cases of pellagra, namely, those of Pellagrin 362 at 360 Brawley Street, in next-door relationship to 177 Farley Avenue and Pellagrin 69, who had her initial erythema some months later at 363 Forest Street, in next-door relationship to 360 Brawley Street.

TABLE 7.—CASES OF PELLAGRA INCIDENT IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1910

House	Residence Period	Pellagrin	Sex	Age
288 Brawley.....	To July.....	201	F	22
360 Brawley.....	To May—death....	362	F	33
100 Burnett.....	To October.....	65	F	51
175 Burnett.....	To June—death....	349	M	50
303 College.....	Entire year.....	348	F	40
153 Duncan.....	Entire year.....	750	F	18
177 Farley.....	To Dec.—death....	371	F	16
334 Forest.....	Entire year.....	194	F	26
363 Forest.....	Entire year.....	69	F	17
134 Montgomery.....	To spring.....	654	F	7
113 Oliver.....	February on.....	749	F	17

The other two new cases arose in houses apparently one removed from next-door relationship to a case of pellagra, namely, those of Pellagrin 750 at 153 Duncan Street and Pellagrin 348 at 303 College Street.

In 1911 many more known cases of pellagra resided in Spartan Mills. This is at once evident from the map for 1911, Figure 6. There were two old pellagrins who escaped recurrence in 1911, Pellagrin 444 at 116 Colton Street, and Pellagrin 654 at 147 Milan Street. There were three old pellagrins with indefinite record in 1911, Pellagrin 237 at 131 Colton Street, Pellagrin 750 at 153 Duncan Street, and Pellagrin 70 at 334 Forest Street. There were seventeen pellagrins with active symptoms in 1911, who had contracted the disease previous to 1911 or elsewhere in 1911. These are shown by open circles on the map and are enumerated in Table 8. There were three additional cases,

AUGUST, 1917

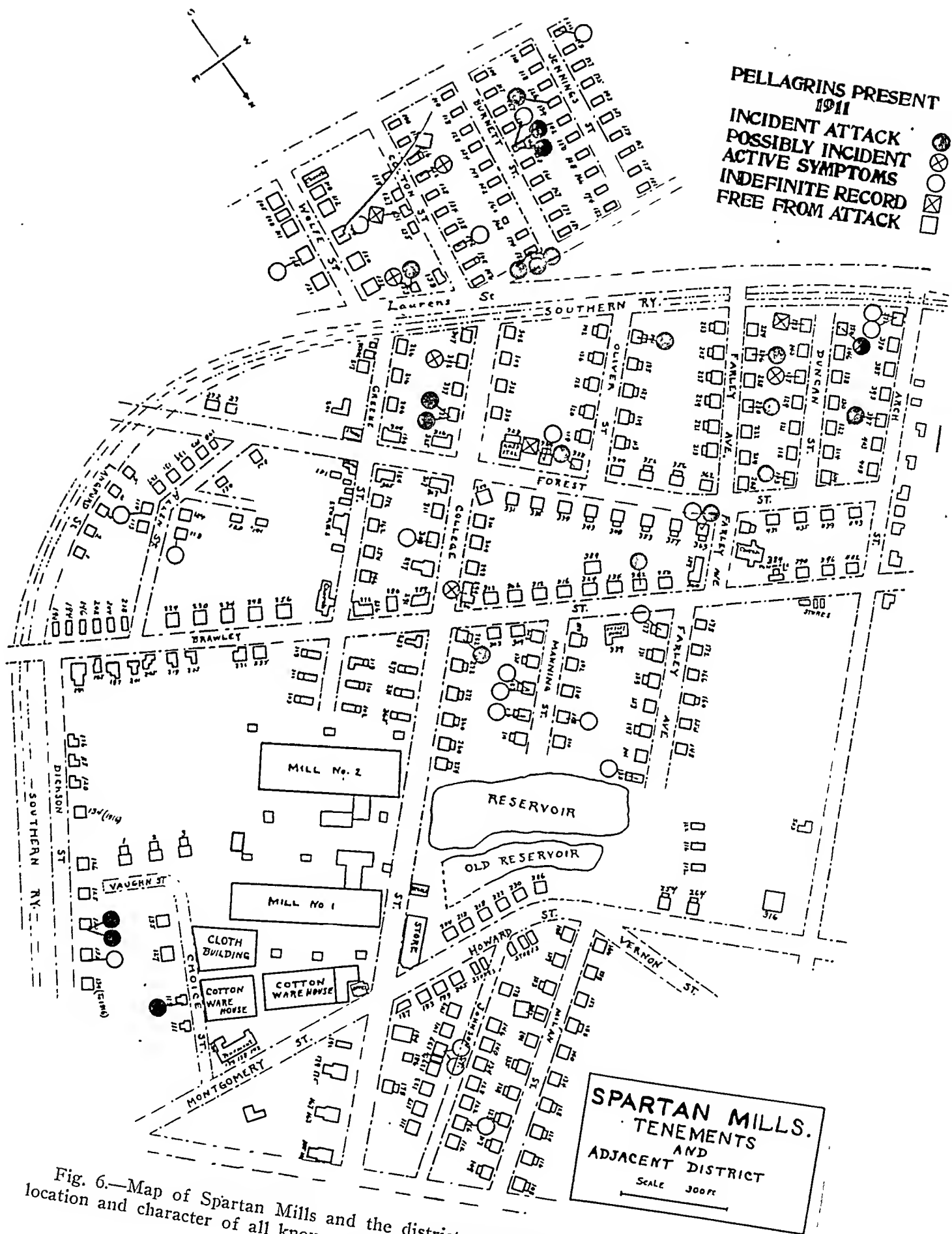


Fig. 6.—Map of Spartan Mills and the district adjacent to it, showing the location and character of all known cases of pellagra present in 1911.

those of Pellagrins 238, 203 and 204, who had initial attacks in this community in 1911 and subsequently moved into other houses here. They are indicated at these later residences by open circles on the map, Figure 6, at 119 Manning Street and 127 Manning Street, to which houses the patients moved in December, 1911.

TABLE 8.—ACTIVE CASES OF PELLAGRA IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1911, BUT NOT INCIDENT HERE IN 1911

House	Residence Period	Pellagrin	Sex	Age
117 Allen.....	To February.....	445	F	26
118 Allen.....	February on.....	445	F	26
371 Arch....	Entire 1911.....	64	M	55
371 Arch....	Entire 1911.....	65	F	52
145 Burnett.....	Feb. to Aug.....	99	F	7
303 College.....	To Jan. 20—death..	348	F	41
142 Colton.....	To Dec.—death....	374	M	7
132 Dickson.....	Entire year.....	515	M	54
133 Farley.....	Entire year.....	115	F	27
177 Farley.....	To spring—death..	372	M	50
334 Forest.....	Entire year.....	194	F	27
363 Forest.....	Entire year.....	69	F	18
111 Jennings.....	April on.....	207	F	26
116 Johnson.....	Entire year.....	11	F	27
137 Johnson.....	Entire year.....	116	F	60
137 Johnson..	Summer only.....	53	F	43
118 Manning.....	November on.....	503	F	43
114 Wolfe.....	Nov. to Dec.....	25	F	39
115 Wolfe.....	December on.....	25	F	39

TABLE 9.—CASES OF PELLAGRA POSSIBLY INCIDENT IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1911

House	Residence Period	Pellagrin	Sex	Age
296 Brawley.....	March on.....	236*	F	36
331 College.....	To October.....	328	F	33
343 College.....	February on.....	198	M	41
122 Colton.....	To March.....	236*	F	36
137 Duncan.....	Spring to Dec.....	238	F	38
153 Laurens.....	To May.....	91	F	34

* This case appears twice in this table because of possible origin at two different houses.

In addition to these there were five active cases of pellagra present in 1911 which may possibly have developed during the patients' residence here. Each of these is designated on the map by a circle containing a cross and the cases are enumerated in Table 9. One of them, that of Pellagrin 236, may possibly have developed at 122 Colton Street or at 296 Brawley Street, as the initial attack appeared within two months after the change of residence. At 122 Colton Street Pellagrin 236 lived in next-door relationship to two houses containing pellagrins and

TABLE 10.—CASES OF PELLAGRA INCIDENT IN DEFINITE HOUSES IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1911

House	Residence Period	Pellagrin	Sex	Age
397 Arch.....	April on.....	105	F	49
342 Brawley.....	To May.....	726	F	25
145 Burnett.....	Feb. to Aug.....	98	F	27
145 Burnett.....	Feb. to Aug.....	100	F	4
182 Burnett.....	Entire year.....	1171	M	9
182 Burnett.....	Entire year.....	1172	F	5
182 Burnett.....	Entire year.....	1173	M	3
119 Cholee.....	Entire year.....	206	F	47
282 College.....	To Sept.—death....	363	F	44
331 College.....	To Oct.—death....	329	F	60
130 Dickson.....	To December.....	203	M	44
130 Dickson.....	To December.....	204	F	37
103 Duncan.....	Entire year.....	232	F	26
154 Duncan.....	Entire year.....	235	M	14
230 Farley.....	To Sept.—death....	1284	F	2
246 Farley.....	Entire year.....	574	F	33
338 Forest.....	Entire year.....	195	F	7
363 Forest.....	Entire year.....	68	F	35
134 Jennings.....	To May.....	555	F	21
153 Laurens.....	To May.....	93	M	6
141 Oliver.....	Entire year.....	748	F	42

this is probably the house of origin. The second patient, Pellagrin 328, moved to Inman Mills late in October 1911 and her initial erythema appeared there early in the spring of 1912. The disease may have been contracted at 331 College Street, Spartan Mills, in 1911. Another of this group, Pellagrin 198, has already been discussed in the group possibly incident in 1910. The fourth patient, Pellagrin 238, came from a neighboring mill village in the spring of 1911 and developed an initial erythema in June. The fifth case, that of Pellagrin 91,

may possibly have been incident at 153 Laurens Street, but the patient's history indicates that she had a somewhat similar illness at 120 Wolfe Street in 1910, although the record is not quite clear. The house at 120 Wolfe Street was in next-door relationship to a pellagrin at 131 Colton Street in 1910.

In 1911 there were twenty-one cases of pellagra which have been recognized as incident in definite houses in this community. These are indicated by solid red circles on the map (Fig. 6) and are enumerated in Table 10. Seven of these cases originated in houses containing another pellagrin, eight arose in houses next door to other pellagrins and six arose in houses apparently farther away than next door from an antecedent case of pellagra.

It is, of course, perfectly obvious from an examination of the map, that the number of persons in this community residing in the same house with a pellagrin early in 1911 was relatively small; that the number living next door was considerably larger and the number living farther away than next door very much larger. This was evidently true in all the years previous to 1911, according to the available records. The data for 1911 and for previous years are, however, far from complete, and we have only very meagre information concerning the non-pellagrous population in these years.

PELLAGRA IN 1912

Our field work in Spartanburg County began in 1912 and in 1913 our first house-to-house census of this community was made. This census has been repeated in 1914, 1915 and 1916. During the pellagra seasons of 1912, 1913 and 1914 we were engaged in field investigations in this community. Our records for this district in 1912 and subsequent years are, therefore, much more complete, not only in regard to pellagrins, but also in regard to the nonpellagrous population.

In our Second Progress Report we attempted to present this material so as to measure the correlation which may exist between the location of one's domicile and his liability to contract pellagra. In that study we divided the nonpellagrous population of this village, there designated as Village Sp, into three groups: first, those nonpellagrous persons residing in the same house with a pellagrin; second, those nonpellagrous persons residing next door to a pellagrin; and, third, those residing in houses farther away than next door from a pellagrin. The persons in each group were then followed to the termination of our records and the number who acquired pellagra in each group was ascertained and by reference to the total number of persons in the group, the ratio of incidence of pellagra in each group for the time covered was calculated. In the present discussion we shall pur-

sue the same general plan, modified in some details so as to adapt it better to the larger mass of data now available and to remove certain features which have been criticized by some of our fellow students and which have seemed to them to be a source of fallacy. In the present study the population of the community in each year will be considered separately, the detailed data in regard to number of persons, period of residence, period of domiciliary exposure, classification of the

SCHEME OF DOMICILE STUDY

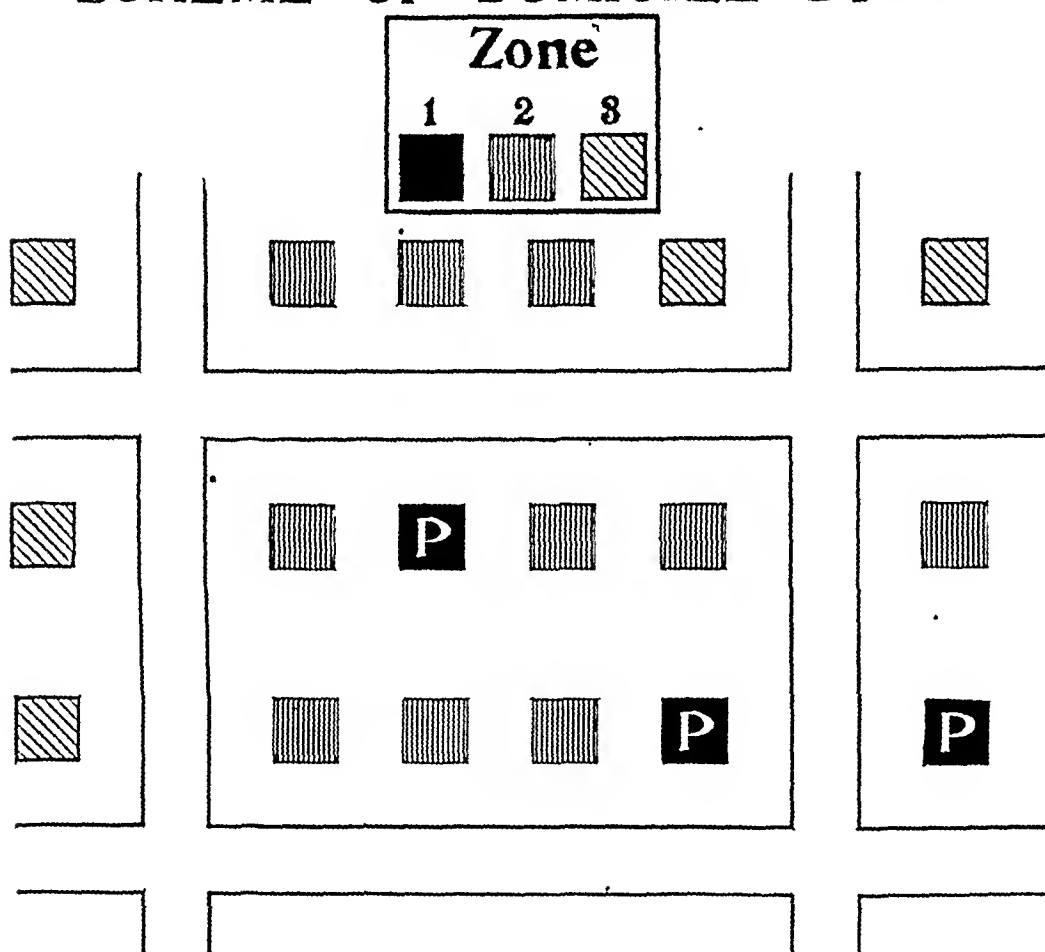


Fig. 7.—Scheme of the domicile study. The black squares with white letters indicate houses in which cases of pellagra already exist. These houses belong in Zone 1. Houses situated next door belong in Zone 2. All houses situated farther away in the same village belong in Zone 3.

population as to residence in Zone 1, Zone 2 or Zone 3, and the subsequent development of pellagra will be presented in tabular form and for each year a map will be presented showing the exact location of each recognized case of pellagra in the community.

The basic scheme of the domicile study is indicated by Figure 7, which is the same as shown in our previous report. A domicile relationship of less than fourteen days has been omitted from considera-

tion. Zone 1 includes all nonpellagrins who lived in the same house with a case of pellagra for at least two weeks in the respective year. Any case of pellagra which developed in these people later than two weeks from the beginning of the domiciliary relationship and within a reasonable period subsequent to its termination, has been credited and tabulated as a case incident in Zone 1. The reasonable period has been selected somewhat arbitrarily as three months in the warmer season, April 1 to October 1, and six months in the colder half of the year, October 1 to April 1. In all probability this interval is too short to include the incubation period of all cases of pellagra, especially in adults, but it would seem to include a considerable proportion of the cases. Obviously, poor judgment in selection of this interval would only obscure any possible correlation which might exist, so that if correlation is shown, the selection of the interval may be regarded as justified for the present purpose, at least. Zone 2 includes all nonpellagrins who lived in a house next door to a case of pellagra for at least two weeks in the respective year. A case of the disease developing in these persons later than two weeks from the beginning of the domiciliary relationship and within three months in summer or six months in winter after its termination has been credited and tabulated as a case incident in Zone 2, unless, on account of a previous residence in a house with a pellagrin within a period of three months in summer or six months in winter, it has been possible to credit the case to Zone 1. In the same way, Zone 3 includes all persons who lived in a house farther away than next door from a pellagrin for a period greater than three months in summer or six months in winter, that is, all persons not assignable to Zone 1 or Zone 2. Cases of pellagra arising in this population have been credited and tabulated as cases incident in Zone 3. In the tables it will be seen that each house has been set down and classified in one zone for the entire year or for part of the year in different zones, according to this scheme. When a family changed zones during the year, its nonpellagrous members have been counted in each zone, but when they changed houses without altering their zone relationship to pellagra, they have not been counted a second time in the same year. When pellagra developed in a person who had changed his residence without altering his zone relationship to pellagra, the case was credited to the second residence, if the erythema appeared later than two weeks after moving.

The data for the year 1912 are presented in Table 20. The records are rather incomplete because the first census was not made until late in 1913, and it was then impossible to ascertain the occupants of all the houses in 1912. It is also very probable that the data for the pellagrins themselves are somewhat incomplete. The available data show twelve

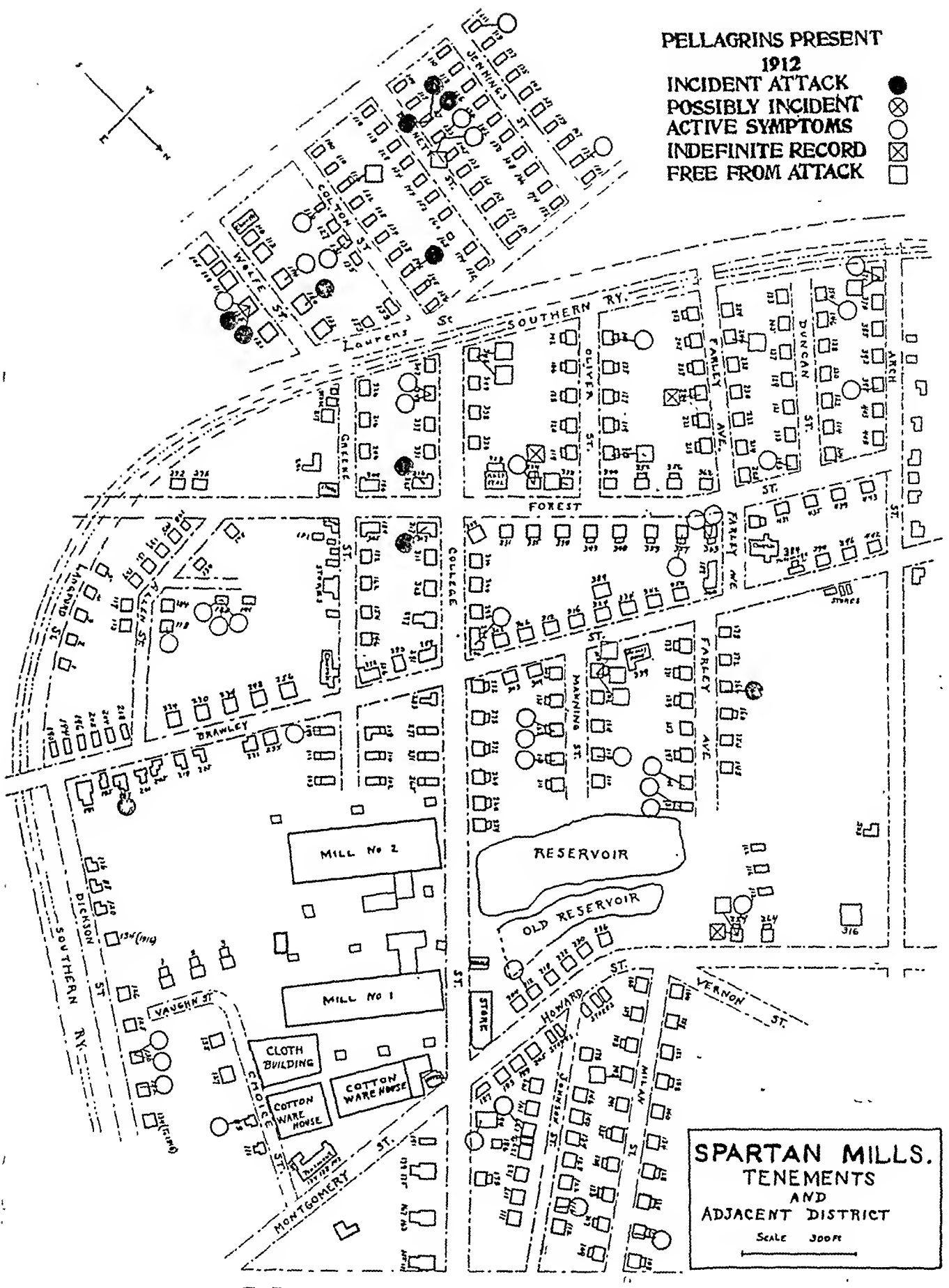


Fig. 8.—Map of Spartan Mills and the district adjacent to it, showing the location and character of all known cases of pellagra present in 1912.

old pellagrins free from symptoms during 1912, three old pellagrins with indefinite record in 1912, and thirty-three old pellagrins with definite attack of pellagra in 1912, the disease having been acquired in a previous year or elsewhere in 1912. Several of these pellagrins changed their residence in the village during 1912 and have, therefore, been indicated on the map at more than one house. Moreover, of the persons with initial attack in 1912, two, namely, Pellagrins 1313 and 1419, moved to another house in the same year and have been designated by hollow circles at 119 Colton Street and 212 Howard Street, respectively. Of the twelve old pellagrins who were free from recurrence in 1912, four had not shown symptoms of the disease for two or more years. These

TABLE 11.—CASES OF PELLAGRA INCIDENT AFTER DOMICILIARY EXPOSURE IN DEFINITE HOUSES IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1912

House	Residence in House	Zone	Residence in Zone	Pellagrin	Sex	Age
197 Brawley.....	Since 1910.....	3	1910—August, 1912	502	F	37
127 Burnett.....	Since winter, 1911....	2	March 1, 1912-spring, 1912..	1290	F	26
127 Burnett.....	Since winter, 1911....	2	March 1, 1912-spring, 1912..	1291	F	7
127 Burnett.....	Since winter, 1911....	1	Spring, 1912-summer, 1912..	1292	F	4
317 College.....	Since 1895.....	3	1895-June, 1912	197	F	38
325 College.....	Since March, 1912.....	2	June, 1912-Aug., 1912.....	1419	M	58
142 Colton.....	Since March, 1910....	3	Dec., 1911-June, 1912.....	443	M	4
141 Farley.....	Since Oct., 1912.....	1	Fall, 1911-Nov. 29, 1912....	1014*	F	6
166 Farley.....	Since 1905.....	3	Early 1911-summer 1912....	893	F	41
115 Wolfe.....	Since Dec., 1911.....	1	April, 1910-June, 1912.....	26	F	13
115 Wolfe.....	Since Dec., 1911.....	1	April, 1910-June, 1912.....	27	M	6
120 Wolfe.....	Since 1910.....	2	1910-spring, 1912	1313	F	49

* The initial erythema appeared early in the spring of 1913 in this case, following an association with the grandmother, Pellagrin 503, from October until her death on Nov. 29, 1912, in the house at 141 Farley Avenue.

are Pellagrins 444, 435, 749 and 654. Although indicated in the tabulations of Table 20, they have been excluded from consideration as active centers in the domiciliary study for the year 1912. The tabulated data for 1912 also show 193 nonpellagrous persons residing in Zone 1, in the same house with a pellagrin, 589 persons in Zone 2, in houses next door to a pellagrin and 700 persons in Zone 3, in houses farther away than next door to a pellagrin. Of these, twelve contracted pellagra here in 1912, according to the available information.

Those pellagrins who suffered initial attacks in 1912 or in 1913, following within a reasonable time after termination of exposure in the first or second zone in 1912, are indicated at their respective residences in Table 20 and further information in regard to them is summarized

in Table 11. In this latter table, the period of residence in the respective houses is shown. The period of exposure in the respective zones, so far as is known, has also been indicated, this period being terminated by onset of the disease in the exposed person or by removal from the zone of exposure. Eleven of the twelve cases are indicated on the map for 1912, Figure 8, and the other one, that of Pellagrin 1014, is indicated on the map for 1913, Figure 9, inasmuch as in this case the initial erythema appeared in 1913. Of the twelve incident cases, four appeared in the population classed in Zone 1, four in Zone 2 and four in Zone 3. Pellagrin 1292, placed in Zone 1, was a girl four years of age when she suffered an initial attack at 127 Burnett Street in the summer of 1912. Her mother, Pellagrin 1290, and sister, Pellagrin 1291, were antecedent pellagrins living in the same house for some months. Her case, therefore, belongs in Zone 1. Pellagrin 1014 was another little girl, aged 6 when her initial erythema appeared early in the spring of 1913. Her grandmother, Pellagrin 503, aged 45, developed pellagra elsewhere in 1911. She and her husband, their daughter and three grandchildren moved to 118 Manning Street, Spartan Mills, later in 1911. Here they remained until July, 1912. Then the whole family moved to a farm a few miles away. At about this time Pellagrin 503 suffered a recurrent attack which gradually became more severe. About the first of October, 1912, she was brought to her father's home, 141 Farley Avenue, Spartan Mills, and she died there on November 29, 1912. At the farm her husband, Pellagrin 502, suffered an initial attack of pellagra early in November, 1912. One grandchild, the little girl here in question, Pellagrin 1014, came with her grandmother to 141 Farley Avenue, where they slept together during the grandmother's last illness, and after the death of the grandmother the little girl remained with her great grandparents, who were people in fair financial circumstances. She developed an initial erythema early in the spring of 1913, about four months after the grandmother's death, and has been designated as a case developing within six months after exposure to pellagra in the fall in Zone 1. In 1914 she suffered a mild recurrence. Pellagrin 26 was a girl aged 13 who had lived with her mother, Pellagrin 25, at 115 Wolfe Street since December, 1911. Her mother had contracted pellagra in 1910 at Columbia and since that time had rigidly excluded cornmeal from the dietary of her family. The mother suffered a recurrence about June 1, 1912, and Pellagrin 26 developed an initial erythema a few days later. Her brother aged 6, Pellagrin 27, suffered an initial attack at the same time. Both of these children have been classed as developing pellagra in Zone 1.

Among the 193 nonpellagrous persons residing in the same house with a pellagrin in 1912 there were, therefore, four who developed the disease at such a time as to be considered incident to this exposure. The indicated incidence rate in this zone in 1912 was, therefore, 2.07 per cent.

In the population of the second zone there were also four incident cases of pellagra. Pellagrin 1290, a woman aged 26 in 1912, suffered a first known attack of pellagra at 127 Burnett Street in the spring of 1912. At the same time her daughter, Pellagrin 1291, aged 7, suffered her first attack. They had moved to this house about November, 1911, and it was situated next door to 135 Burnett Street, in which Pellagrins 64 and 65 resided after March 1, 1912. Later in 1912 a second daughter, Pellagrin 1292, suffered an initial attack in the same house. She has been considered as a case incident in Zone 1. Another case in the second zone was Pellagrin 1419, a man aged 58 in 1912. He resided at 325 College Street, next door to Pellagrin 197 at 317 College Street. Pellagrin 197 developed an initial erythema in June, 1912, and Pellagrin 1419 had an initial erythema about the middle of August, 1912, within a few days after he had moved from 325 College Street to 212 Howard Street. The fourth case in the second zone, Pellagrin 1313, was a woman aged 49, who developed an initial erythema at 120 Wolfe Street in the spring or summer of 1912. She had been living there since 1910 in next-door relationship to Pellagrin 237 at 131 Colton Street and to Pellagrin 25 at 115 Wolfe Street.

The nonpellagrous population exposed in the second zone in 1912, shown in Table 20, numbered 589, so that the indicated rate of incidence in this zone was 0.68 per cent.

There were also four incident cases of pellagra in the third zone, in whom the initial attack of pellagra was developed in a house farther away than next door from an antecedent case of the disease. The first case, Pellagrin 202 at 197 Brawley Street, was a woman aged 37 who had lived in this same house since 1910. Early in August she had an erythema on the forearms, chiefly on the right, after washing clothes out-of-doors. When seen on August 30, the forearms were slightly scaly, but the eruption was not considered characteristic of pellagra. At that time she was accepted as a case of pellagra with some reservation. She was not seen again by us. Her neighbors stated that this woman was not considered to be a pellagrin by them. The second third-zone case was that of Pellagrin 197, a woman aged 38, who had an initial erythema about June 1, 1912, at 317 College Street. The diagnosis is certain in her case, as she was seen with recurrence in subsequent years. The residence in which she appears to have developed the disease was a large two-family house with

numerous occupants, some of them transient and unrecorded. The house was situated in next-door relationship to the Good Samaritan Hospital, in which pellagrins were occasionally treated. We have decided, however, not to consider the hospital as a zone center because its sanitary condition was entirely different from that of the residences. This patient has, therefore, been assigned to the third zone. The third case placed in this zone was that of Pellagrin 443, a boy aged 4, who had an initial erythema at 142 Colton Street in June, 1912, where he had lived since March, 1910. His brother, aged 9, Pellagrin 374, died of pellagra in the same house in December, 1911. The exact day of December on which Pellagrin 374 died and the exact day of June on which the erythema appeared in Pellagrin 443 are unknown. The interval is approximately six months, more than two of which belonged to the warmer season. Pellagrin 443 has, therefore, been assigned to the third zone, although there can be little question of the relation between his case and the earlier one in the family. The fourth case placed in Zone 3 was that of Pellagrin 893, a woman aged 41, at 166 Farley Avenue. She was socially intimate with Pellagrin 68 at 363 Forest Street, who frequently took meals at 166 Farley Avenue in 1912. According to the rules adopted for this study, however, Pellagrin 893 has been placed in the third zone. It will be noted that three of the four third-zone cases were those of women over 35 years of age, persons in whom intervals between recurrent attacks are prone to be most irregular, as shown in a previous paper, and in whom, we are convinced, the length of incubation period may often be much longer than that assumed for this study, namely, six months. Furthermore, women of this age are the most frequent visitors in these mill-village communities, especially visitors of the sick. The one child placed in Zone 3, Pellagrin 443, has already been considered and it is evident that his case might, with equal justice, have been assigned to Zone 1.

The total population in Zone 3 in 1912, according to Table 20, numbered 700. The indicated incidence rate in this zone was, therefore, 0.57 per cent., not significantly different from the rate in Zone 2.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1913

The data of the domiciliary study for the year 1913 are presented in Table 21. The first census was made in August and September of that year and the census data are more complete than for the year 1912, but somewhat less complete than for the following years. The records of pellagra cases in 1913 are also more reliable than for 1912, but less complete and trustworthy than in 1914. There were present in 1913, according to available information, twenty-four old pellagrins free from symptoms, three old pellagrins with indefinite record in 1913

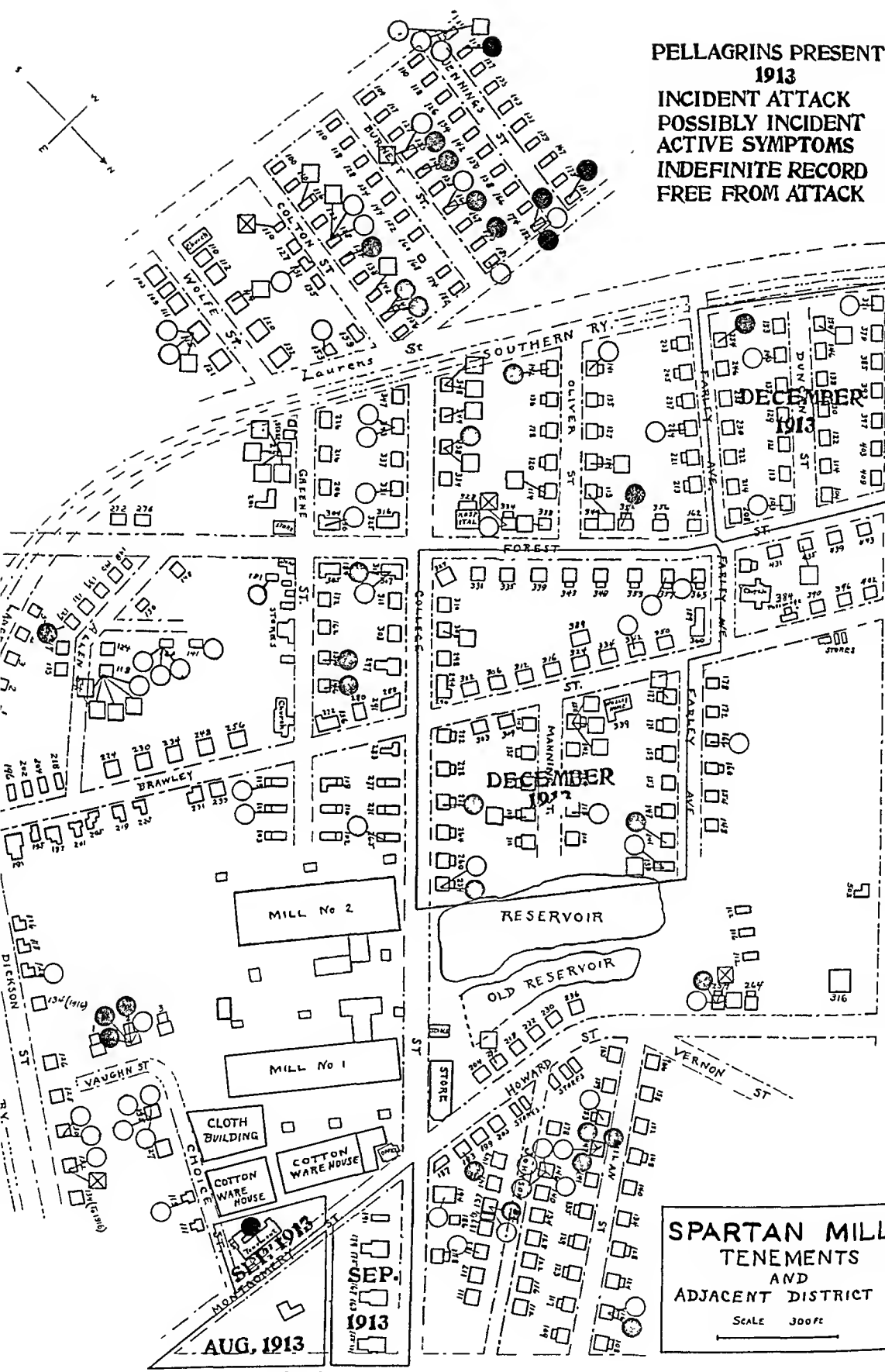


Fig. 9.—Map of Spartan Mills and the district adjacent to it, showing the location and character of all known cases of pellagra present in 1913. The portions enclosed by the red lines were equipped with water-carriage sewer connections in 1913, the month of installation being indicated in red.

and forty-two pellagrins with active symptoms in this year, the initial attack having appeared in a previous year or elsewhere in 1913. Because some of these changed their residences within the community during 1913, one pellagrin may appear on the map in more than one place. In five instances a pellagrin living in Spartan Mills in 1913 moved into another house subsequently and is shown there as an open circle on the map, one at 331 College Street, one at 120 Dickson Street and three at 135 Choice Street, and the same three again at 146 Johnson Street. Of the twenty-four pellagrins who were without recurrence in 1913, there were ten who had been free from symptoms for two years. These are Pellagrins 444, 749, 860, 195, 1171, 1172, 1173, 435, 625 and 626; the cases are indicated in Table 21, but are excluded from consideration as active centers in the study of domiciliary relationship in 1913.

According to the data of Table 21, 427 persons lived in the same house with a pellagrin in 1913, so as to be assigned to Zone 1; 1176 persons lived next door, so as to be assigned to Zone 2 and 925 persons lived farther away than next door, so as to be assigned to Zone 3. In the entire population of the three zones there developed thirty-three new cases of pellagra in 1913, one of them within six months after termination of a first-zone exposure in 1912 and, therefore, assigned to the 1912 group, Pellagrin 1014 in Table 11. The remaining thirty-two cases of pellagra incident in 1913, together with an additional case, that of Pellagrin 1267 at 331 College Street, who developed an initial erythema early in January, 1914, in this same house where she had been living with a pellagrin since July, 1913, are enumerated in Table 12. In accordance with the available information, fifteen of these incident cases have been assigned to Zone 1, twelve to Zone 2 and six to Zone 3. The cases in each of these groups will be considered in turn.

Pellagrin 295, a woman aged 22, suffered an initial erythema in May, 1913, at 135 Burnett Street, where she had been boarding with Pellagrins 64 and 65 since March. Pellagrin 736, a girl aged 4, had an initial erythema in July, 1913, at 161 Burnett Street, where she had been living with her grandmother, Pellagrin 703, since March. Pellagrin 989, a woman aged 27, had an initial erythema in June, 1913, at 317 College Street, where she had been living with her mother for eleven years. Her mother, Pellagrin 197, had suffered from the disease since 1912. The fourth case in this zone was that of a woman, Pellagrin 1267, aged 28, who had been living at 331 College Street since June, 1912. Pellagrin 796, with active symptoms, moved into this house in July, 1913. Pellagrin 1267 developed her initial erythema early in January, 1914, at this house, and has, therefore, been assigned to Zone 1 in 1913. The fifth case was that of a woman, Pellagrin 438,

TABLE 12.—CASES OF PELLAGRA INCIDENT AFTER DOMICILIARY EXPOSURE IN A DEFINITE HOUSE IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1913

House	Residence in House	Zone	Residence in Zone	Pellagrins	Sex	Age
127 Allen.....	Since 1910.....	3	Feb., 1911-Feb., 1913.....	740	M	50
135 Burnett.....	Since March, 1913....	1	1912-May, 1913	295	F	22
145 Burnett.....	Since Feb., 1913.....	2	Feb., 1913-spring, 1913.....	1337	F	55
161 Burnett.....	Since Dec., 1912.....	1	March, 1912-July, 1913.....	736	F	4
175 Burnett.....	Since 1910.....	2	Jan., 1913-May, 1913.....	1312	F	19
254 College.....	Since Oct., 1912.....	3	Oct., 1912-May 1, 1913.....	796	F	32
272 College.....	Since Oct., 1912.....	2	Oct., 1912-May, 1913*.....	738	F	42
317 College.....	Since 1902.....	1	June, 1912-June, 1913.....	989	F	25
331 College.....	Since June, 1912.....	1	July, 1913-Jan., 1914.....	1267†	F	28
338 College.....	Since March 1, 1913..	2	March 1, 1913-June, 1913....	739	F	7
134 Colton.....	Since April, 1912.....	2	April, 1912-Aug. 1, 1913....	742	F	41
148 Colton.....	Since 1902.....	2	June, 1912-summer, 1913....	868	F	19
148 Colton.....	Since 1910.....	2	June, 1912-summer, 1913....	1376	F	20
254 Farley.....	Since 1912.....	3	1912-June, 1913	583	M	67
352 Forest.....	Since 1908.....	2	Fall, 1912-Dec., 1913.....	904	F	25
146 Greene.....	Since Jan., 1913.....	3	Jan., 1913-June, 1913.....	1134	M	28
154 Greene.....	Since Feb., 1913.....	3	1909-June 1, 1913.....	548	F	5
193 Howard.....	Since 1905.....	2	Spring, 1912-summer, 1913..	590	F	27
254 Howard.....	Since Oct., 1912.....	1	March, 1910-June 1, 1913....	488	F	21
119 Jennings.....	Since March., 1913....	2	Mar., 1913-May, 1913.....	650	M	10
181 Jennings.....	Since Jan., 1913.....	2	Dec., 1912-July, 1913.....	1167	F	21
182 Jennings.....	Since 1908.....	1	April 1, 1913-May 17, 1913..	530	M	53
182 Jennings.....	Since 1908.....	1	April 1, 1913-May, 1913.....	1228	F	51
137 Johnson.....	Since Jan. 19, 1909....	1	Spring, 1909-May, 1913.....	552	F	24
116 Milan.....	Since Feb., 1912.....	1	1911-Feb., 1913	520	F	39
147 Milan.....	Since spring, 1911....	1	Jan., 1913-June, 1913.....	651	M	2
147 Milan.....	Since spring, 1911....	1	Jan., 1913-June, 1913.....	652	M	4
147 Milan.....	Since spring, 1911....	1	Jan., 1913-June, 1913.....	653	M	7
134 Montgomery..	Since April, 1912.....	3	April, 1912-May, 1913.....	718	F	42
142 Oliver.....	Since 1907.....	2	May 1, 1911-Aug., 1913.....	747	F	44
2 Vaughn.....	Since Feb. 18, 1913....	1	July, 1911-April, 1913.....	510	F	19
2 Vaughn.....	Since Feb. 18, 1913....	1	July, 1911-May, 1913.....	512	F	38
2 Vaughn.....	Since Feb. 18, 1913....	1	July, 1911-Sept., 1913.....	737	F	9

* Pellagrins 738 developed an initial erythema in June, 1913. Pellagrins 238 lived next door to her until May, 1913.

† Pellagrins 1267 developed an initial erythema early in January, 1914, at 331 College Street, where she had been living in the same house with a pellagrins since July, 1913.

aged 21. She had an initial erythema in June, 1913, at 254 Howard Street, where she had been living with her mother, Pellagrin 437, and two other pellagrins since October, 1912. Pellagrin 530 was a man aged 53, who had been living at 182 Jennings Street since 1908. On April 1, 1913, his son-in-law, Pellagrin 529, who had come down with an initial attack of pellagra at another mill village on March 28, 1913, was received into the home of the father-in-law to be cared for. On May 17, 1913, about six weeks after this pellagrin arrived, the father-in-law had his initial erythema and he died of pellagra on July 16, 1913. His wife, Pellagrin 1228, aged 52, had an initial erythema at about the same time as her husband and died early in 1914, apparently without recurrence of pellagra. These two patients, together with the one across the street, Pellagrin 1167, at 181 Jennings Street, are of some interest because they had been living in the same house for more than six years and Pellagrin 1167, their son's wife, had been living at 181 Jennings Street since September, 1912. With the entrance of a pellagrous son-in-law to their family circle, three of them promptly developed pellagra. They are also interesting because there was no blood relationship in the group of four patients. The eighth case in Zone 1 was Pellagrin 552, a woman aged 24. She had been living at 137 Johnson Street since January 19, 1909, with her husband and his mother. This mother, Pellagrin 116, had been a pellagrin since 1909. The ninth case was that of a woman, Pellagrin 520, aged 39, who had been living with her father, Pellagrin 519, at 116 Milan Street since February, 1912. The father had suffered from this disease since 1911. His daughter had an initial erythema in February, 1913, and died of pellagra in July, 1913. Pellagrins 651, 652 and 653 were brothers aged 2, 4 and 7, respectively. They lived at 147 Milan Street from early in 1911 to October 29, 1913. Their sister, aged 10, Pellagrin 654, had an initial attack in 1910, escaped recurrence in 1911 and 1912, but suffered a recurrent attack in June, 1913. Her three little brothers developed an initial erythema in June, 1913. The thirteenth case in Zone 1 was that of a girl, Pellagrin 510, aged 19, who lived at 2 Vaughn Street from February, 1913, to the spring of 1914, in the same house with Pellagrin 511, her father. He had been a pellagrin since 1911. The daughter suffered an initial erythema in April, 1913. Her mother, aged 38, had an initial erythema in May, 1913, in the same house. She is designated as Pellagrin 512. Another girl in the same family, Pellagrin 737, aged 9, had an initial erythema in the same house in September, 1913. These fifteen newly incident cases of pellagra appeared in a total recorded exposed population of 427 persons in Zone 1, so that the incidence rate of this zone in 1913 was 3.51 per cent.

The twelve incident cases assigned to the second zone will be briefly reviewed next. Pellagrin 1337, a woman aged 57, suffered an initial erythema at 145 Burnett Street in the spring of 1913. She had been living there since February, 1913. Her residence was next door to 135 Burnett Street, in which Pellagrins 64 and 65 resided throughout 1913. The second case in Zone 2, Pellagrin 1312, was a married woman aged 19, who had lived at 175 Burnett Street since 1910. During 1913 she helped nurse Pellagrin 508, next door at 181 Burnett Street, until she died in May, 1913. About this time her own hands showed an erythema for the first time. The third case was that of a woman, Pellagrin 738, aged 42, who lived at 272 College Street from October, 1912 to August, 1914, next door to 119 Manning Street, in which Pellagrin 238, with onset in 1911, lived until May, 1913. Pellagrin 738 had an initial erythema in June, 1913. The fourth case in this zone was that of a girl, Pellagrin 739, aged 7, who lived at 338 College Street from March 1, 1913 to August, 1913, next door to Pellagrins 198 and 328 at 343 College Street. The little girl developed a sore mouth and diarrhea in June, 1913, and a pellagrous erythema on July 10, 1913. The fifth case in Zone 2 was that of a woman, Pellagrin 742, aged 41, who had lived at 134 Colton Street since April, 1912. This house was next door to active pellagrins at 128 and 131 Colton Streets. She had an initial erythema about August 1, 1913. The sixth case was that of a girl, Pellagrin 868, aged 19, who had lived at 148 Colton Street since 1902. In 1912 a case of pellagra, that of Pellagrin 443, appeared next door at 142 Colton Street and remained there throughout 1913. In the summer of 1913 Pellagrin 868 had her initial erythema. The seventh case was that of an unrelated woman, Pellagrin 1376, aged 20, who had lived in this same house since 1910. She also had an initial erythema in the summer of 1913. The eighth case in Zone 2 was that of a woman, Pellagrin 904, aged 25, who had lived at 352 Forest Street since 1907. This house was in next-door relationship to Pellagrin 68 at 357 Forest Street. The first erythema of Pellagrin 904 appeared late in December, 1913, and there was a recurrent attack in April, 1914. The ninth case in Zone 2 was that of a woman, Pellagrin 590, aged 27, who had resided at 193 Howard Street since 1905. Since 1912 this house had been in next-door relationship to Pellagrin 105 at 194 College Street. The first erythema of Pellagrin 590 appeared in the summer of 1913. The tenth case was that of a boy, Pellagrin 650, aged 10. He lived at 119 Jennings Street from March, 1913, to August, 1913, next door to Pellagrin 207 at 111 Jennings Street. In his case the initial erythema appeared in May, 1913. The eleventh case in Zone 2 was that of Pellagrin 1167 at 181 Jennings Street. She was a woman aged 21, the daughter-in-law of Pellagrin

530, just across the street. Her case has been discussed along with his in the preceding paragraph. Pellagrin 747, whose case was the twelfth and last case in this zone, was a woman aged 44, who had lived at 142 Oliver Street since 1907, across the street from Pellagrin 748 at 141 Oliver Street. In her case the initial erythema appeared in August, 1913. The total population exposed in Zone 2 in 1913, according to Table 21, numbered 1176. The twelve incident cases give, therefore, an incidence rate of 1.02 per cent. in this zone in 1913.

The cases of pellagra incident in Zone 3 were six in number. Pellagrin 740 at 127 Allen Street was a man aged 50, who had lived in this house since 1910. In February, 1913, he had a definite attack of pellagra. His previous history is very incomplete and indefinite, but he did have a somewhat similar attack in 1895 and he had suffered from dysentery every summer for many years. His case has been designated as incident in 1913 in Zone 3. In the second case, that of Pellagrin 796, a woman aged 32, the initial erythema appeared at 254 College Street on May 1, 1913. She had lived there since October, 1912. From 1907 to October, 1912, she had resided at 317 College Street, where Pellagrin 197 lived at the same time. The interval between the termination of the residence in this house and the onset of initial erythema at the new residence was slightly more than six months, and the case has, therefore, been credited to Zone 3. The third case was that of a man, Pellagrin 583, aged 67, who resided at 254 Farley Avenue with his son in 1913. Just when his son moved there is not definitely known, but it was some time between September, 1912 and February, 1913. The father, Pellagrin 583, spent his time in rotation at four different residences, living with his sons and daughters, and the exact time of residence at each house was not ascertained. He suffered his initial erythema about June 15, 1913, and died of pellagra on July 25, 1913. In the absence of further information, his case has been considered as incident at 254 Farley Avenue and, therefore, in the third zone. The fourth case was that of a man, Pellagrin 1134, aged 28, who lived at 146 Greene Street from early in 1913 to August, 1913, and had an initial attack of pellagra there about June, 1913. This man was not seen by us until September, 1914, at which time he was suffering from a definite recurrent attack of pellagra. The attack in 1913 was reported to us in that year by his physician. Before coming to Spartan Mills this man had lived in the same house with Pellagrin 447 in a neighboring mill village and, according to the report of his physician in 1913, his case would seem to be properly classed as incident in this previous residence. However, his case has been designated as incident at 146 Greene Street because of some uncertainty as to the exact time he moved there. In the fifth case, that of a girl, Pellagrin 548, aged 5,

the initial erythema appeared about June 1, 1913, at 154 Greene Street, next door to the preceding case. She lived there from February, 1913, to October, 1913. Previously, from 1909 to February, 1913, she had lived at 2 Langford Street, concerning the environment of which, in 1913 and previously, we have only fragmentary information. This case might possibly be placed in Zone 2, next door to Pellagrin 1134, if the information about him were more definite. As it is, both of these cases have been placed in Zone 3. The sixth case was that of a woman, Pellagrin 718, aged 42, who objected to being interviewed. She lived at 134 Howard Street from April 10, 1912, to September, 1913. She gave a very reluctant history of erythema in May, 1913, and she has, therefore, been assigned to the third zone. Of these six cases placed in the third zone in 1913, there was one, that of Pellagrin 796, in which the history was fairly definite and complete. The other five

TABLE 13.—COMPARISON OF THE RESULT OF THE PREVIOUS DOMICILE STUDY OF SPARTAN MILLS WITH THE PRESENT STUDY OF THE SAME COMMUNITY FOR THE SAME YEARS

	Zone 1			Zone 2			Zone 3		
	In- stances of Expo- sure ₁	Inci- dent Pella- grins	Inci- dence %	In- stances of Expo- sure	Inci- dent Pella- grins	Inci- dence %	In- stances of Expo- sure	Inci- dent Pella- grins	Inci- dence %
Previous study	199	14	7.04	779	3	0.38	838	6	0.72
Present study									
1912	193	4	2.07	589	4	0.68	700	4	0.57
1913	427	15	3.51	1,176	12	1.02	925	6	0.65
Both years	620	19	3.06	1,765	16	0.91	1,625	10	0.62

examples are instances of unsatisfactory and incomplete records. The total exposed population of Zone 3 in 1913, according to Table 21 was 925 persons. The indicated incidence rate in this group was, therefore, 0.65 per cent., considerably less than that of Zone 2.

Spartan Mills is the same community designated as Village Sp in our Second Progress Report. Our data in relation to domicile in this village up to the end of 1913 were briefly presented in that report. At that time we possessed for this community only the data accumulated by our field study of pellagra in 1912 and 1913 and the one census made late in 1913. The records in regard to this village were considered to be much less complete than the records for the other five villages used in that study. Table 100* of that report showed a summary of the data then available, which is reproduced here in Table 13, along with

* THE ARCHIVES INT. MED., 1914, 14, 362; Second Progress Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate Medical School and Hospital, New York, 1915, p. 85.

the summarized data of the present study for the years 1912 and 1913. It will be noted that the previous study had shown a higher incidence in the third zone than in the second zone, a relationship quite opposite to what we found in all the other five villages studied. We recognized at that time that our data for this village were less complete than for the others. Subsequent work has added much information, so that the total recorded population has been considerably increased and that in Zone 1 in 1913 has become more than double what it was before. The number of cases of pellagra incident in the second zone has increased from three to sixteen. Even our present records are not definite enough in regard to the history and environment of some of the cases, particularly those which have still been assigned to Zone 3. The time to learn and record the facts in an epidemiologic study is the time in which the events to be correlated are actually taking place. After the people have moved away, died, or forgotten the exact facts and especially the exact dates, an inquiry among the population yields only partially satisfactory results. Recognizing the shortcomings of our records for this village in 1913 and before, we undertook to make them more complete and reliable in the subsequent years. This was the more readily accomplished because the confidence of the people had been gained by the earlier work and, in addition, we already possessed the records of a preceding year to build on.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1914

The data of the domiciliary study for the year 1914 are shown in Table 22. There were present in this community in that year, according to the records, thirty-two old pellagrins free from symptoms, seven old pellagrins with indefinite record for the year and fifty-one pellagrins with active pellagra in 1914, in whom the disease first appeared in a previous year, or elsewhere in 1914. On the map, Figure 10, these pellagrins are designated at the houses in which they resided and one pellagrin in some instances lived in more than one house during the year, so that the figures just mentioned do not correspond in number to the pellagrins located on the map. In four instances a pellagrin incident in Spartan Mills in 1914 moved into another house in the same community during the year and is indicated at this subsequent residence by an open circle on the map, one at 134 Milan Street, two at 120 Oliver Street and one at 172 Greene Street. There were four cases of pellagra incident in 1914, which have been indicated on the map as possibly incident in two different houses, 348 College Street and 236 Howard Street. According to the rules adopted for this domiciliary study, these four cases must be classed as incident in the second zone at 348 College Street, although the initial eruptions appeared early in

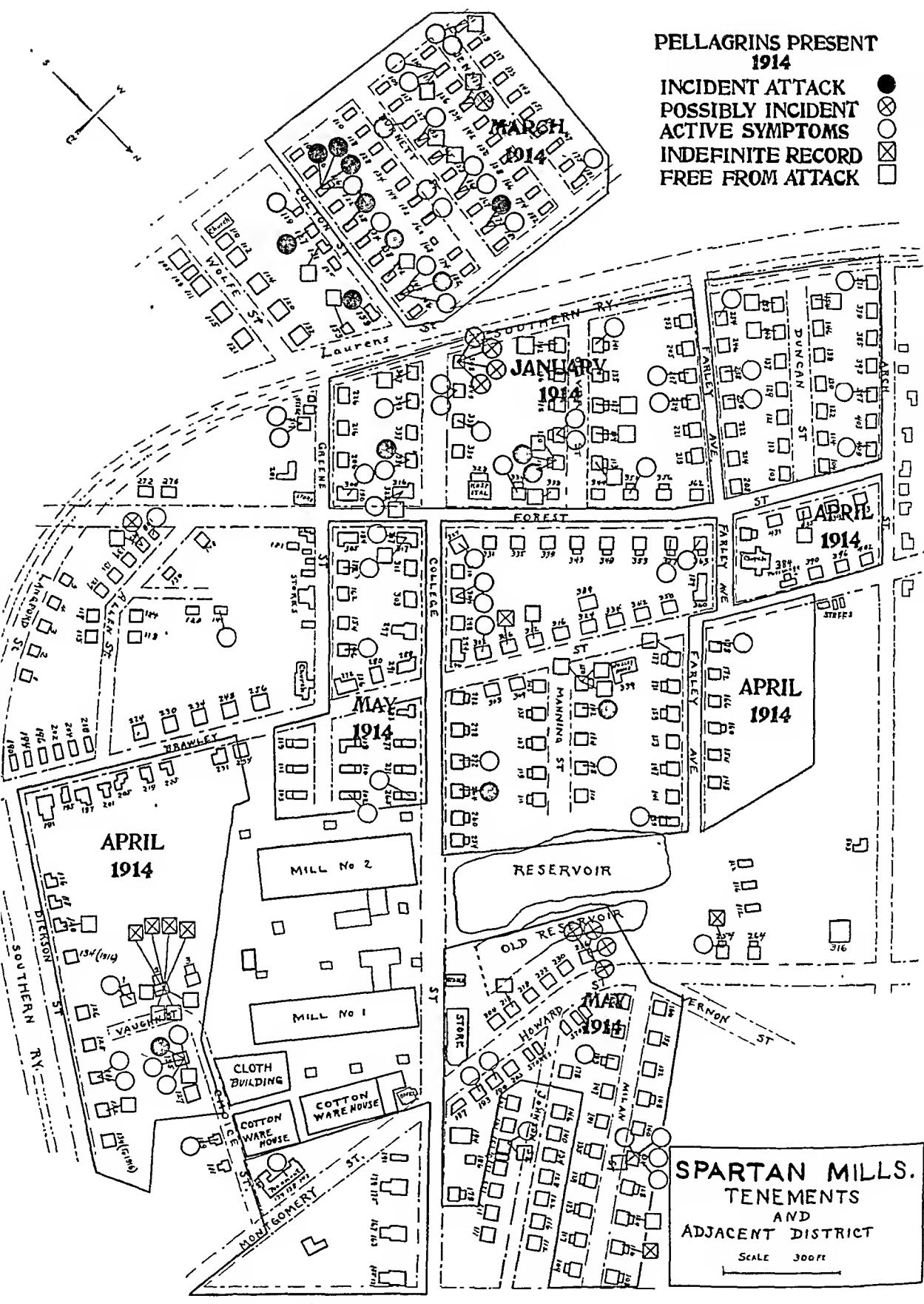


Fig. 10.—Map of Spartan Mills and the district adjacent to it, showing the location and character of all known cases of pellagra present in 1914. The portions enclosed within red lines were equipped with water-carriage sewer connections in 1913 or 1914. For those equipped in 1914, the month of installation is indicated on this map in red.

May, after moving to 236 Howard Street on Feb. 15, 1914. Of the thirty-two pellagrins without recurrence in 1914, nineteen had remained free from symptoms for two years; these were Pellagrins 65, 443, 235, 238, 232, 195, 1292, 1255, 1171, 1172, 1173, 749, 625, 626, 1419, 261, 263, 264 and 265. These cases appear in Table 22, but have been excluded from consideration as centers in the domicile study for 1914.

TABLE 14.—CASES OF PELLAGRA INCIDENT AFTER DOMICILIARY EXPOSURE IN A DEFINITE HOUSE IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1914

House	Residence in House	Zone	Residence in Zone	Pella-grin	Sex	Age
145 Allen.....	Since June, 1914.....	1	Spring, 1912-July, 1914.....	1289	F	9
175 Burnett.....	Since July 1, 1914....	1	July 1, 1914-July 23, 1914..	1026	F	1½
135 Cholee.....	Since Dec. 1, 1913 ...	1	Jan., 1913-June 2, 1914.....	1005	F	31
264 College.....	Since March 1, 1914...	2	March 1, 1914-spring, 1914..	1174	M	36
348 College.....	Since Dec. 18, 1913....	2	Dec. 18, 1913-Feb. 15, 1914*..	917	F	30
348 College.....	Since Dec. 18, 1913....	2	Dec. 18, 1913-Feb. 15, 1914*..	918	M	10
348 College.....	Since Dec. 18, 1913....	2	Dec. 18, 1913-Feb. 15, 1914*..	919	M	9
348 College.....	Since Dec. 18, 1913....	2	Dec. 18, 1913-Feb. 15, 1914*..	920	M	5
116 Colton.....	Since March, 1914.....	1	Jan., 1914-May 8, 1914.....	913	F	6
116 Colton.....	Since March, 1914.....	1	Jan., 1914-June 10, 1914.....	939	F	42
116 Colton.....	Since March, 1914.....	1	Jan., 1914-summer, 1914....	1309	F	21
127 Colton.....	Since 1908.....	2	Spring, 1909-summer, 1914..	1389	M	50
128 Colton.....	Since Feb. 15, 1914....	2	Feb. 15, 1914-summer, 1914..	1305	F	36
138 Colton.....	Since 1909.....	2	June, 1912-summer, 1914...	1310	F	9
149 Colton.....	Since 1902.....	1	Summer, 1913-spring, 1914..	912	F	39
134 Jennings.....	Since March 15, 1914..	2	March 15, '14-March 30, '14.	944	F	23
159 Laurens.....	Since Nov. 15, 1912....	2	Summer, 1913-May 1, 1914..	940	F	66
142 Manning.....	Since June, 1911.....	3	Jan., 1913-June, 1914.....	1269	F	33
114 Oliver.....	Since Dec., 1913.....	2	Dec., 1913-Jan. 21, 1914.....	977	F	22
114 Oliver.....	Since Dec., 1913.....	2	Dec., 1913-Jan. 21, 1914.....	1259	M	4

* Pellagrins 917, 918, 919 and 920 moved out of Zone 2 on Feb. 15, 1914. They all developed the initial erythema in the period from May 1 to May 14, 1914.

According to the data of Table 22, there were 427 nonpellagrous persons living during 1914 in the same house with a pellagrin in whom the disease was active in either 1913 or 1914, or both years; these exposed nonpellagrous individuals have been assigned to Zone 1. There were 1,144 nonpellagrous persons living not in a house in Zone 1, but next door to such a house, so as to be assigned to Zone 2 and there were 1,050 persons living farther away than next door from any pellagrin with active attack in 1913 or 1914, so as to be assigned to Zone 3. In the entire population of the three zones there developed twenty new cases of pellagra in 1914. These are enumerated in Table 14.

The cases of pellagra incident in Zone 1 numbered seven. Pellagrin 1289 at 145 Allen Street was a girl aged 9, who had lived in this house with her mother, Pellagrin 328, for only about two weeks when she developed an initial erythema in the summer of 1914. Previously the family had been living outside the community. This case is classed as incident at 145 Allen Street with some reservation, because of the very short period of residence previous to onset in this house. The second case in Zone 1, at 175 Burnett Street, was a girl baby, Pellagrin 1026, aged 20 months, who developed an initial erythema on July 23, 1914. She was a daughter of Pellagrin 529 and had lived at 182 Jennings Street in 1913, where her father lay ill with pellagra and both her maternal grandparents, Pellagrins 530 and 1228, contracted the disease. After the death of her grandfather and father, she lived with her pellagrous grandmother at 120 Dickson Street from August, 1913, to February, 1914, when her grandmother died, and at 186 College Street in next-door relation to Pellagrins 116 and 552 from February to May 15, 1914. From May 15 to July 1 she was at 174 Burnett Street, another house in Zone 2. She then came to 175 Burnett Street on July 1 and developed an initial erythema on July 23. At this last house she was being cared for by Pellagrin 1312 and her case has, therefore, been designated as incident there in Zone 1, although with some reservation, because of the short period of her residence there. The disease did not recur in 1915 or 1916 in this little child. The third case in Zone 1, at 135 Choice Street, was that of a woman, Pellagrin 1005, aged 31, who developed an initial erythema on June 2, 1914. She had four young pellagrous children, Pellagrins 651, 652, 653 and 654, one having acquired the disease in 1910 and the others in 1913. The family moved to 134 Milan Street in the fall of 1914. Four of the five pellagrins in this family suffered attacks in 1914, three of them again in 1915, but they all escaped without recurrence in 1916. The fourth case in Zone 1, at 116 Colton Street, was that of a woman, Pellagrin 939, aged 42, who had lived in this house since 1910. Her daughter, Pellagrin 444, aged 10 in 1914, had been a pellagrin since 1907 and her husband had died of pellagra in 1910. The little girl, Pellagrin 444, had a recurrent attack of pellagra in 1914 and in the same house her mother, Pellagrin 939, and her two sisters, Pellagrin 913, aged 6, and Pellagrin 1309, aged 20, suffered initial attacks of the disease, all in Zone 1. The seventh case in Zone 1, at 148 Colton Street, was that of a woman, Pellagrin 912, aged 39, who had lived in this same house since 1902. Her daughter, Pellagrin 868, and an unrelated woman, Pellagrin 1376, both pellagrins since 1913, were living in the same house.

The total exposed population in Zone 1, according to Table 22, was 427 persons, so that the seven incident cases indicate an incidence rate of 1.64 per cent. in this zone in 1914.

There were twelve incident cases of pellagra in the population of the second zone in 1914. Pellagrin 1174 at 264 College Street was a man aged 36, who had lived there since March 1, 1914, next door to Pellagrin 738 at 272 College Street. Previously, he had resided in other mill villages in houses, the environment of which has not been examined. In his case the initial erythema appeared in the spring or summer of 1914 at 264 College Street and he has been considered as incident there, with some reservation. Pellagrins 917, 918, 919 and 920, a woman aged 30, and three sons, aged 10, 9 and 5, respectively, all developed an erythema for the first time within two weeks, from May 1 to May 14, 1914, at 236 Howard Street. They had lived in this house since February 15, 1914. From 1909 to September, 1913, this family had lived in one house at a neighboring mill village. A portion of this same house was occupied by another family from 1911 to July 1, 1913, and the wife in this family, Pellagrin 593, had an initial attack in 1912, so that Pellagrins 917, 918, 919 and 920 were in the same house with a pellagrin up to July 1, 1913. They were also next door to Pellagrin 282 in this same village until they moved away in September, 1913. From September to December 18, 1913, they lived in Spartanburg in a house not near pellagrins, so far as we have been able to ascertain. From December 18, 1913 to February 15, 1914, they lived at 348 College Street, next door to Pellagrin 726 at 344 College Street, Pellagrin 198 at 343 College Street and Pellagrin 747 at 142 Oliver Street. During their residence here, the construction work of installing the water-carriage sewer system and the removal of the surface privies was performed in this section, the sewer connections being made in January, 1914. In all four cases in this family the initial erythema developed within three months after moving from this house to 236 Howard Street and within such a brief interval that no one case can be placed in Zone 1 in relation to any of the others, according to the rules of this study. These cases are, therefore, considered as incident in Zone 2 within three months after exposure at 348 College Street, which, considering the season of the year, may not be an unreasonably long incubation period even for young children. The other possibility we have had in mind was that the mother may have contracted pellagra the previous year without recognizing it and that the children were then secondary to her in Zone 1 at 236 Howard Street in 1914. This appeared to be the more plausible explanation of these cases, but proof of it could not be obtained.

The sixth case in Zone 2, at 127 Colton Street, was that of a man, Pellagrin 1389, aged 53, a fairly well-to-do carpenter who had lived at this house since 1908, next door to pellagrins at 116, 119 and 131 Colton Street. He appeared to be very well nourished and weighed

more than 200 pounds. He indulged somewhat freely in alcohol, as we have frequently observed to be the case in other instances of pellagra in well-to-do men. In his case the erythema seems to have appeared in the summer of 1914, although it may possibly have been a year earlier. The disease recurred in 1915, according to his history, and he was seen with typical eruption in 1916. His case has been classed as certainly incident in the second zone, and probably in 1914. The seventh case, at 128 Colton Street, was that of a woman, Pellagrin 1305, aged 36, who had lived there since Feb. 15, 1914. Previously she had lived in the mountains of North Carolina. At 128 Colton Street she was next door to pellagrins at 131 and 134 Colton Street. During the summer of 1914 she had a mild erythema, to which she paid little or no attention. She was then pregnant. In February or early in March, 1915, she had a severe recurrence. The eighth case, Pellagrin 1310 at 138 Colton Street, was a girl aged 9, who had been living in this house since 1909. In 1914 her residence was next door to active pellagrins at 134 Colton Street and 160 Burnett Street. She had a mild attack of pellagra in the summer of 1914 and a recurrence in 1915. The ninth incident case in Zone 2, at 134 Jennings Street, was that of a woman, Pellagrin 944, aged 23. She moved to this house from Greenville County, S. C., on March 15, 1914, and her initial erythema appeared on March 30, 1914, so that her case is just barely classifiable as incident in this house, according to the plan of this domicile study. Her mother, Pellagrin 1255, lived with her at the former residence and here also. The mother had an initial attack in 1910 with recurrence in 1911, but had been free from recurrence since that time. For that reason, she cannot be considered as a center of distribution in this domicile study. Next door, at 135 Burnett Street, Pellagrin 64 had active pellagra in 1914, so that this new case, Pellagrin 944, has been classed as incident in the second zone. This has been done with considerable reservation because of the very brief period of residence. It seems very probable that the disease was actually contracted at the previous residence in Greenville County, but information in regard to the situation there was not obtainable. The tenth case, at 159 Laurens Street, was that of a woman, Pellagrin 940, aged 66, who had lived in this house since November 15, 1912, next door in 1913 and 1914 to Pellagrin 328 at 153 Laurens Street, and to Pellagrins 868 and 1376 at 148 Colton Street. She developed an initial erythema on May 1, 1914. These two houses on Laurens Street, 153 and 159, were not sewered. In the eleventh and twelfth cases, those of Pellagrin 1259, a boy, aged 5, and his mother, Pellagrin 977, aged 22, initial attacks of pellagra occurred about the same time in June, 1914, at 120 Oliver Street, shortly after the mother and boy moved there from 114 Oliver

Street. They lived at 114 Oliver Street from December, 1913, to June, 1914, next door to 334 Forest Street, in which Pellagrin 70 suffered a recurrent attack beginning August, 1913 and ending in death on Jan. 21, 1914. Both this boy and his mother suffered an initial attack about the same time and both have, therefore, been classified in the second zone.

The total exposed population in Zone 2, according to Table 22, numbered 1,144 persons. With twelve incident cases in this population, the indicated incidence rate for Zone 2 in 1914 was 1.05 per cent.

In the third zone only one incident case arose in 1914, that of Pellagrin 1269. She was a woman aged 33 who had lived at 142 Manning Street since June, 1911, and was still there in 1916. A physician informed us in 1914 that he had attended her in childbirth in August, 1913, and that in June, 1914, while talking with her on the street, he had observed a typical pellagrous erythema on her hands and forearms. She was interviewed by us at her home in August, 1913, June, 1914, August, 1915, and August, 1916. Our records show that a son was born in June, 1913, (not August) and another son in March, 1916. We have not been able to obtain any history of pellagra from her nor have we seen any signs of it. In 1914, when she was said to have pellagra, her weight was approximately 200 pounds. Her mother, Pellagrin 237 at 131 Colton Street, had been a pellagrin for many years and she was at her house frequently. Next door, at 150 Manning Street, Pellagrins 1171, 1172 and 1173 had been living for some years, but they had been free from recurrence of the disease since the initial attack in 1911 and have not been considered as centers of distribution in 1914. The case of Pellagrin 1269 has, therefore, been designated as incident in the third zone in 1914, with considerable reservation, especially in regard to the diagnosis.

According to the data of Table 22, the total population of Zone 3 in 1914 numbered 1,050 persons, so that the indicated incidence rate in this zone in 1914 was 0.10 per cent. The more complete data of 1914 have served to reduce the incidence in Zone 3 practically to the vanishing point.

On the map of the community for 1914, Figure 10, the districts sewered in 1913 are enclosed in red lines without any included date. The sections sewered in 1914 are also enclosed in red lines and the month in which the sewer installation was made is indicated in each such enclosed section. If one cares to look up in the text the incident cases of pellagra located on this map, with particular attention to the period of exposure and the exact date of initial erythema, he may already perceive a distinct indication of the influence of the sewer installation on the incidence of pellagra.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1915

The data of the domiciliary study for the year 1915 are shown in Table 23. There were present in 1915 in this community, according to the records, forty-one old pellagrins free from symptoms. Of this number there were twenty-one who had remained free from recurrence for two years. These were Pellagrins 1337, 893, 194, 1283, 235, 232, 548, 493, 1419, 435, 1292, 1171, 1172, 1173, 654, 749, 747, 261, 263, 264 and 265. They are indicated in Table 23, but have been excluded from consideration as active centers in the domicile study for 1915. There were eight old pellagrins with indefinite record for the year and fifty-four with active attack in 1915, the initial attack having occurred in a previous year or elsewhere in 1915. The houses in which these pellagrins lived during 1915 are indicated in Figure 11. Pellagrin 1282,

TABLE 15.—CASES OF PELLAGRA INCIDENT AFTER DOMICILIARY EXPOSURE IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1915

House	Residence in House	Zone	Residence in Zone	Pella-grin	Sex	Age
127 Burnett.....	Since April, 1915.....	2	Nov., 1914 - June, 1915.....	1303	F	20
152 Burnett.....	Since Nov., 1914.....	1	Birth - June 1, 1915.....	1301	M	3
175 Burnett.....	Since 1910.....	1	May, 1913 - summer, 1915...	1311	M	5
265 College.....	Since Dec., 1914.....	1	Birth - May 28, 1915.....	1276	F	2
334 College.....	Since Nov., 1914.....	2	May 15, 1914 - July, 1915...	1280	F	28
119 Colton.....	Since 1912.....	1	Spring, 1912 - June, 1915...	1314	M	53
110 Greene.....	Since March, 1915.....	2	March - June 15, 1915.....	1279	F	37
172 Greene.....	Since Oct., 1914.....	1	May 1, 1914 - June, 1915.....	1282	F	35
217 Greene.....	Since Jan., 1915.....	2	June 10, 1914 - May, 1915....	1285	F	17
126 Jennings.....	Since May, 1913.....	2	May, 1913 - April, 1915.....	1336	F	31

incident at 172 Greene Street in 1915, moved to 217 Greene Street in September, 1915, and is designated there by an open circle on the map. A second case, Pellagrin 1285, incident at 217 Greene Street, moved in September, 1915, to 347 College Street.

According to Table 23, there were 439 nonpellagrous persons living during 1915 in the same house with a pellagrin in whom the disease was active either in 1914 or 1915, or both years, and these exposed nonpellagrous individuals have been assigned to Zone 1. There were 1,174 nonpellagrous persons living next door to such a house, so as to be assigned to Zone 2, and there were 1,069 persons farther away than next door from any pellagrin with active attack in 1914 or 1915, so as to be assigned to Zone 3. In the entire population of the community there appeared ten new cases of pellagra, which have been designated

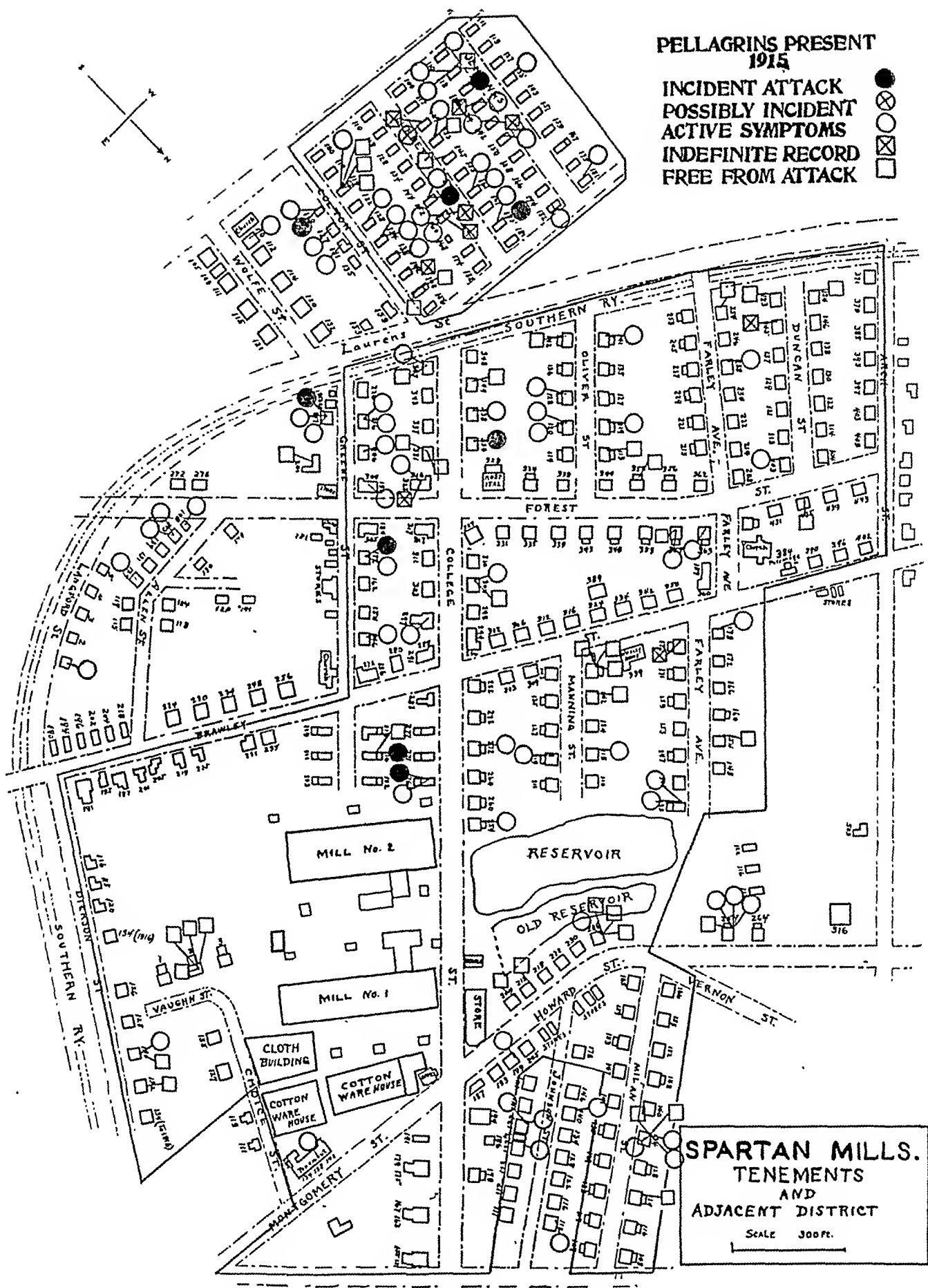


Fig. 11.—Map of Spartan Mills and the district adjacent to it, showing the location and character of all known cases of pellagra present in 1915. The sewered districts are enclosed within red lines.

as cases incident in this community in 1915, according to the assumptions made for this study. These ten cases are enumerated in Table 15.

Five of these cases fall into Zone 1. Pellagrin 1301 at 152 Burnett Street was a boy aged 3, who had lived in this house since November, 1914. He was born at 343 College Street in 1912, moved to 160 Burnett Street in April, 1914, and to 152 Burnett Street in November, 1914. He had a severe intestinal disturbance in May, 1915, and his feet "turned brown" about June 1 and remained so for about two weeks. He was taken to the Pellagra Hospital of the U. S. Public Health Service for examination, where the condition was considered as probably pellagra, but a positive diagnosis could not be made. There was no recurrence in 1916. The diagnosis in this case appears, therefore, rather uncertain. His father, Pellagrin 198, lived in the same house and suffered a recurrent attack of pellagra in 1915, so that the case of the child has been assigned to Zone 1. Pellagrin 1311 at 175 Burnett Street was a boy aged 5, who had lived in this house since 1910 with his mother, Pellagrin 1312. In the summer of 1915 an erythema appeared on the dorsal surfaces of his feet. He was not seen by a physician, so far as we are aware, and the nature of this erythema may be questioned. In 1916 he remained free from manifestations of pellagra. He has been tentatively accepted as a pellagrin incident in Zone 1 in 1915. The third case in Zone 1 was that of Pellagrin 1276, a girl aged 2, who resided at 265 College Street from December, 1914 to June, 1915. Her mother, Pellagrin 987, had an initial attack in May, 1908, with recurrence every year. From March, 1914 to July, 1914, the family lived at 102 Greene Street in Spartan Mills. Then they went to a farm in Tennessee. About Christmas time, 1915, they returned to this community and lived at 265 College Street. Here the mother suffered a very severe recurrent attack of pellagra about May 1, in which there was marked mental disturbance. There was no one competent to look after the household and, according to the neighbors, the house and premises were in a filthy condition. In the latter part of May the mother was committed to the Columbia State Hospital for the Insane. The baby, Pellagrin 1276, developed a sore mouth on May 19, and an erythematous eruption on the backs of the hands, forearms and feet, accompanied by diarrhea, on May 28, 1915. She was received as a patient into the Pellagra Hospital of the U. S. Public Health Service on June 19, 1915, where she remained until April 16, 1916. The mother remained in Columbia only about six weeks, was brought back to Spartan Mills on July 1, 1915, and on July 10, 1915, was taken from there to her mother's home in Tennessee to die, according to the neighbors. She had to be carried to the train. In 1916 both mother

and child visited Spartan Mills and both appeared to be fully recovered. We have no further record of them after April, 1916. The case of the child, Pellagrin 1276, has been designated as incident in Zone 1 at 265 College Street in 1915. The fourth case in Zone 1, at 119 Colton Street, was that of a man, Pellagrin 1314, aged 53, who had lived there since 1912. Previously, from 1910 to 1912, he resided at 120 Wolfe Street. He was away from home during the entire month of February, 1915, when he was employed in the Du Pont Powder Works at Du Pont, Virginia. He then returned home and resumed his regular occupation as a carpenter. His wife, Pellagrin 1313, had an initial attack of the disease in 1912 and suffered recurrence in 1914 and 1915. The husband suffered an initial erythema in June, 1915, and his case has been designated as incident in Zone 1 at 119 Colton Street. The fifth case in Zone 1, at 172 Greene Street, was that of a feeble-minded woman, Pellagrin 1282, aged 35. Definite pellagrous eruption was observed on her forearms by us, August 6, 1915, and this "sunburn" seems to have appeared in June, 1915. The patient was rather uncommunicative and denied ever having any symptoms or signs of pellagra, nor was it possible to gain the information from other members of the household. Her mother, Pellagrin 940, lived in the same house. In fact, they had lived together for many years at various houses. In 1914 they resided at 159 Laurens Street, where the mother had a first recognized attack of pellagra. It seems very doubtful whether Pellagrin 1282 had a first attack in 1915 or not. Her mental attitude and that of the family justifies a strong suspicion that this woman may have had pellagra for several years. In the absence of definite history, the observed pellagrous eruption in 1915 has to be taken as the first erythema. The family lived at 172 Greene Street from October, 1914, to September, 1915, and the case of Pellagrin 1282 has, therefore, been designated as incident in Zone 1 in this house in 1915, although with considerable reservation.

Of these five cases in Zone 1, there were only three in which the diagnosis may be considered certain, those of Pellagrins 1301 and 1311 being regarded as doubtful cases. Of the three definite pellagrins, one, Pellagrin 1282, may have had the disease in previous years. There remain two cases incident in Zone 1 in this community in 1915 with a fair degree of certainty, Pellagrin 1276 at 265 College Street and Pellagrin 1314 at 119 Colton Street. The total exposed nonpellagrous population in Zone 1 in 1915 numbered 439 persons, so that the origin of five cases in this zone gives an indicated incidence rate of 1.14 per cent. for 1915. One of these incident cases arose in the district adjacent to Spartan Mills proper, in which the first zone population in 1915 numbered forty-seven persons, giving an incidence rate of 2.13 per

cent. The other four cases appeared in the mill district proper in a total of 392* exposed persons, giving an incidence rate of 1.02 per cent. in the first zone for 1915.

In Table 15 the five cases of pellagra incident in Zone 2 in 1915 are enumerated. Pellagrin 1303 at 127 Burnett Street was a woman aged 20. She was married, but resided with her mother, a widow. The family lived in Greenville, S. C., from May, 1914 to November, 1914. Then they moved to Spartanburg County to Mill Village Sa., where they lived next door to Pellagrins 1321 and 1322, from November, 1914, to the spring of 1915. The mother and most of the family moved to 127 Burnett Street, Spartan Mills, in February, 1915, but the one daughter, Pellagrin 1303, and her husband and child remained at the former residence until April, 1915, and she, Pellagrin 1303, developed a very sore mouth, accompanied by pyrosis, in March at this former residence. In April she also came to 127 Burnett Street and early in June the pellagrous erythema appeared on her hands. This latter residence was next door to active pellagrins in 118 and 134 Jennings Street and 135 Burnett Street, so that, under the arbitrary rules of this domicile study, the case of Pellagrin 1303 has been designated as incident in Zone 2 at 127 Burnett Street. There is considerable probability, however, that the disease was actually contracted at the previous residence. The second case in Zone 2, at 334 College Street, was that of a woman, Pellagrin 1280, aged 28, who had the earliest recognized erythema early in June, 1915. From November, 1913, to November, 1914, she had lived at 3 G Street at Inman Mills, in next-door relationship to Pellagrin 934, after May 15, 1914. In the spring of 1914 she had severe digestive disturbance and her doctor told her he thought she had pellagra. An erythema was not observed in that year. She became pregnant in September, 1914. The family moved to 334 College Street, Spartan Mills, in November, 1914. Early in the spring of 1915 the patient had "scalded mouth" and the pellagrous erythema appeared early in July, about two weeks after childbirth, which occurred on June 21, 1915. The eruption was seen by us on August 6, 1915. In September she was admitted as an outpatient for dietetic treatment at the Pellagra Hospital of the U. S. Public Health Service, where the diagnosis was confirmed. She took meals there for three or four months. In March, 1916, she moved to Chesnee, S. C., where she suffered a recurrent attack of pellagra in July, 1916. At 334 College Street she lived next door to active pellagrins at 338 College Street and at 120 Oliver Street. Her case has, therefore, been designated as incident in the second zone at this residence, although there is a strong

*This number includes four persons living with Pellagrins 436, 437 and 438, at 254 Howard Street, which was an unsewered mill house.

suspicion that the disease was contracted at Inman Mills in 1914, and the incubation period prolonged on account of pregnancy. The third case in Zone 2, at 110 Greene Street, was that of a woman, Pellagrin 1279, aged 37. She lived there since March, 1915, having resided previously in a neighboring district of Spartanburg City. Her residence at 110 Greene Street was in next-door relationship to 265 College Street, in which Pellagrin 987 had a severe recurrence, with mental involvement in 1915. Neither of these residences was screened. The daughter of Pellagrin 1279, aged 7, had suffered an initial attack of pellagra in 1913, without any recurrence in 1914 or 1915. She cannot be considered as a center for distribution of pellagra in 1915. The financial condition of this family had improved very much since 1913. In that year the husband and father was in legal difficulties and unable to contribute anything to the support of his wife and three small children. The wife worked in the mill and the children were cared for by neighbors. In 1915 the husband was working steadily in the mill and the wife was caring for the home and family. Pellagrin 1279 had an initial erythema on June 15, 1915, and her case has been designated as incident in Zone 2 at 110 Greene Street in 1915, although the brief period of residence, March to June 15, suggests the possibility that the disease may have been contracted at the previous residence outside of this community. The fourth case in Zone 2, at 217 Greene Street, was that of a married woman, Pellagrin 1285, aged 17. She lived at 148 Colton Street from 1901 to 1914, her mother and sister being pellagrins in this same house. In the spring of 1914 she married and went to North Carolina, returning in June, when she stayed about a week at her mother's house. She then lived in several different houses during the next six months, always next door to a pellagrin, but did not again live in the same house with an active pellagrin. About January 1, 1915, she moved to 217 Greene Street. This house had just been vacated by Pellagrin 1293, who had a prolonged recurrent attack in 1914, and it was just across the street from Pellagrins 328 and 1289 at 216 Greene Street and from the new residence of Pellagrin 1293 at 206 Greene Street. Pellagrin 1285 gave birth to a boy on Feb. 14, 1915. An initial erythema appeared some time in May, 1915. Her case has been designated as incident in the second zone at 217 Greene Street. The fifth case in Zone 2 was that of a woman, Pellagrin 1336, 31 years old, who had resided at 126 Jennings Street since May, 1913. This house was next door to active pellagrins at 118, 134 and 135 Jennings Street and 135 Burnett Street. In her case the initial erythema appeared in April, 1915, and she was seen by us with a recurrent eruption in August, 1916. This patient had spent a week early in March, 1915, at the home of her father on a farm. He

had been a pellagrin since 1909 and another of his daughters, aged 16, had an initial attack of pellagra in 1914. Early in March his wife, mother of Pellagrin 1336, was severely ill with gastro-intestinal disturbance and it was at this time that Pellagrin 1336 spent the week there. If she had spent two weeks at her father's house at this time, her case would have to be designated as incident there in the first zone, but according to the rules we are following in this study, her case has been designated as incident in Zone 2 at 126 Jennings Street.

In this group of five cases all were women, and the domicile relationship of pellagra was obscured somewhat by changes from one house to another and by pregnancy and childbirth. The cases of Pellagrins 1279 and 1285 seem to be most definitely incident at the residences designated. The exposed population in Zone 2 in 1915 numbered 1,174 persons, so that five incident cases in this zone give an incidence rate of 0.43 per cent. for the year. Of this number, 996 * persons lived in the mill village proper, in which four cases of incident pellagra appeared in 1915, giving an incidence rate of 0.40 per cent. In the district adjacent to Spartan Mills there were 178 persons living in Zone 2 in 1915, with one incident case of pellagra, giving an incidence rate of 0.56 per cent. for that section.

There were no known cases of pellagra incident in Spartan Mills in 1915 in Zone 3, that is in a house farther away than next door from a pellagrin active either in 1914 or 1915, or both years. The total exposed population in this zone in 1915 numbered 1,069 persons, of whom 856 † lived in the mill village proper and 213 resided in the adjacent district. The incidence rate among them for 1915 was zero.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1916

The data for the domiciliary study for 1916 are shown in Table 24, and the location of domicile of each pellagrin is indicated on the map, Figure 12. In 1916 sixty-five old pellagrins free from symptoms were present in this community. This number includes thirty-four pellagrins who had remained free from recurrence for two years. These are Pellagrins 64, 1267, 1167, 796, 893, 913, 939, 868, 912, 204, 1283, 1287, 235, 1174, 904, 232, 548, 493, 918, 919, 920, 1292, 1269, 1171, 1172, 1173, 654, 1005, 749, 747, 261, 263, 264 and 265. They appear in Table 24, but have been excluded from consideration as active centers in the domicile study for 1916. This number does not include Pellagrins 1382 and 1383 at 138 Duncan Street, who moved into Spartan Mills in August, 1916, too late to be considered in the studies for

* This number includes thirteen persons living in unsewered mill houses at 112 Farley Avenue, 122 Farley Avenue and 264 Howard Street.

† This number includes twenty-nine persons living in unsewered mill houses at 116 Farley Avenue, 122 Farley Avenue and 316 Howard Street.

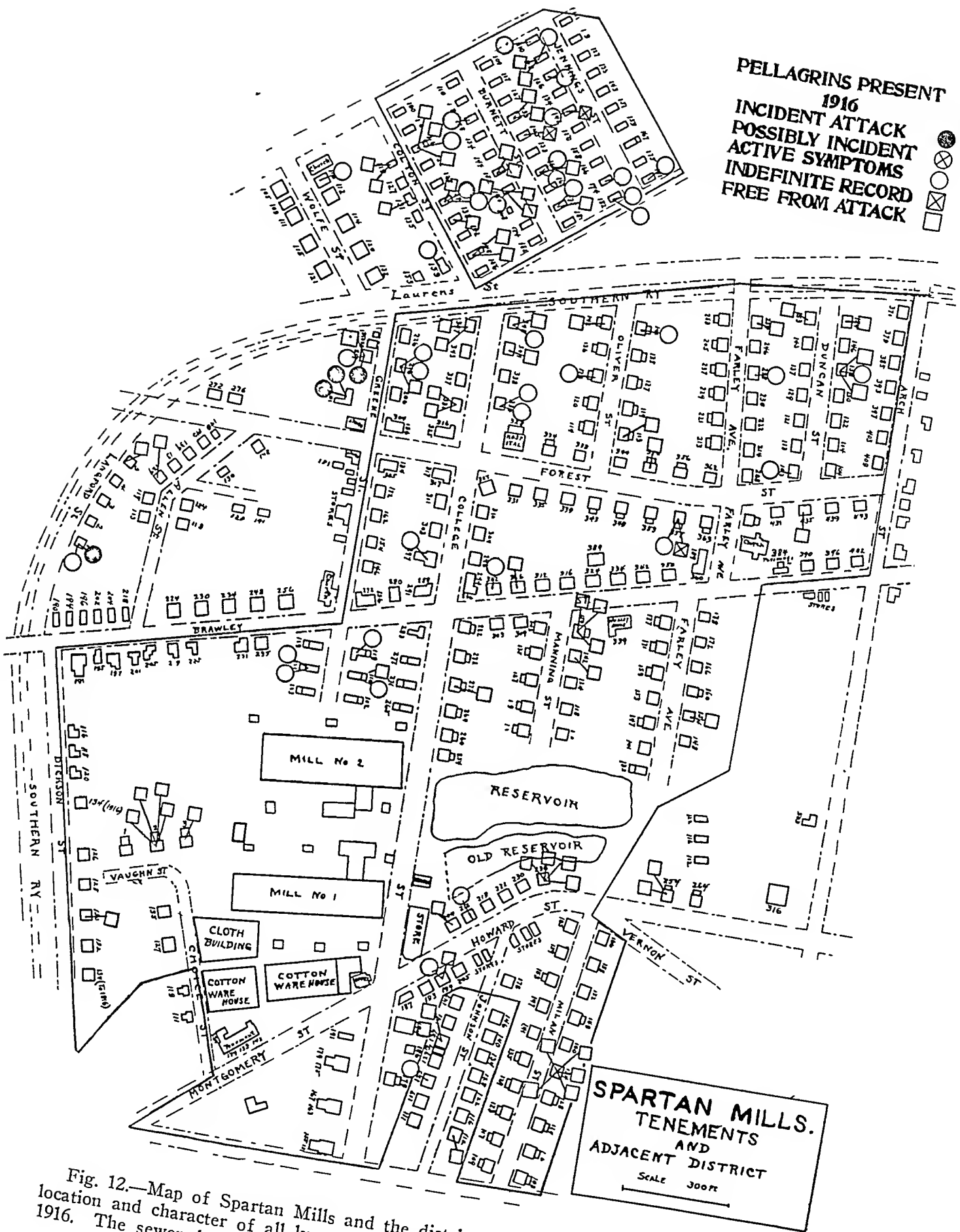


Fig. 12.—Map of Spartan Mills and the district adjacent to it, showing the location and character of all known cases of pellagra present up to Aug. 15, 1916. The sewered districts are enclosed within red lines.

that year. They have, however, been indicated in the tabulation and on the map. There were also present three old pellagrins with indefinite record for the year and thirty-two with active attack in 1916, the initial attack having occurred in a previous year or elsewhere in 1916. Pellagrins 1371 and 1372, who moved into Spartan Mills in August, 1916, have been excluded from this number, although they have been indicated on the map at 111 Greene Street. The houses in which all these pellagrins resided are indicated on the map for this year, Figure 12. Two pellagrins incident in this community in 1916 moved to other houses within the district subsequently and are designated at the second residence by an open circle in each instance. Pellagrin 1351, who was incident at 217 Greene Street, subsequently moved to 216 Greene Street and Pellagrin 1353, who was incident at 1 Langford Street, subsequently moved to 181 Jennings Street.

TABLE 16.—CASES OF PELLAGRA WITH ONSET PREVIOUS TO AUG. 15, 1916, INCIDENT AFTER DOMICILIARY EXPOSURE IN SPARTAN MILLS AND ADJACENT DISTRICT IN 1916

House	Residence in House	Zone	Residence in Zone	Pellagrin	Sex	Age
134 Colton.....	Since June 30, 1915....	1	June 30, 1915-June, 1916....	1377	F	18
201 Greene.....	Since Dec. 22, 1914....	2	Nov., 1915-June, 1916.....	1399	F	11
201 Greene.....	Since Dec. 22, 1914....	2	Nov., 1915-June, 1916.....	1400	F	13
217 Greene.....	Since Sept. 2, 1915....	1	May 1, 1914-June, 1916.....	1351	F	21
1 Langford.....	Since Nov. 1, 1915....	1	May, 1915-April, 1916.....	1353	F	33

According to Table 24, there were 215 nonpellagrous persons living during 1916 in the same house with a pellagrin in whom the disease was active either in 1915 or 1916, or both years; these persons have been assigned to Zone 1. There were 1,006 nonpellagrous persons living next door to such a house, so as to be assigned to Zone 2, and 940 persons living farther away than next door from any pellagrin with active attack in 1915 or 1916, so as to be assigned to Zone 3. Those instances in which domiciliary relationship began later than July 1, 1916, have been excluded from consideration in the present study. In the entire population of the community, five incident cases of pellagra appeared in 1916, up to the time of our survey in August. These incident cases of pellagra are enumerated in Table 16.

Three of these cases fall into Zone 1. Pellagrin 1377 at 134 Colton Street was a woman aged 18. She had lived with her father at 128 Burnett Street from December, 1914, to June 30, 1915. She then married and came to live with her husband and his mother at 134 Col-

ton Street. She bore a child on April 21, 1916, and the initial pellagrous erythema appeared about July 15, 1916. Her mother-in-law, Pellagrin 742, suffered attacks of the disease in 1913, 1914 and 1915, but escaped without attack in 1916. Another woman living in the same house, Pellagrin 1376, aged 23, had an initial attack in 1913 and suffered recurrence every year. In 1916 the erythema recurred in March and there was a further exacerbation in June. This woman had lived in this house since September, 1915. Pellagrin 1377 has, therefore, been assigned to Zone 1. It may be noted, however, that 134 Colton Street, which was a sewered house, was in next-door relationship to 131 Colton Street, an unsewered house, in which Pellagrin 237 had resided for many years and in which she had a recurrent attack of pellagra late in 1915. The second case in Zone 1, at 217 Greene Street, was that of a married woman, Pellagrin 1351, aged 21. She had lived with her grandmother, Pellagrin 940, for several years and they resided at 172 Greene Street from October, 1914 to September, 1915. In September, 1915, they moved to 217 Greene Street. Pellagrin 1351 gave birth to a child on Sept. 17, 1915. In her case, the initial pellagrous erythema appeared in June, 1916. In the following month she separated from her grandmother and took the house across the street at 216 Greene Street. The third case in Zone 1, at 1 Langford Street, was that of a married woman, Pellagrin 1353, aged 33. Her husband had been a patient in the State Hospital for the Insane since January, 1914, and she was a factory worker, but did not work in the cotton mill. During 1915 she boarded with Pellagrin 16 at 304 Forest Street, and in 1916 she was boarding with this same family at 1 Langford Street. They moved on Nov. 1, 1915. Pellagrin 16 had an initial attack in 1908 and recurred every year to and including 1916. Pellagrin 1353 had an initial erythema on April 1, 1916, was admitted as a house patient at the Pellagra Hospital on June 3, 1916, and discharged on August 3, 1916. She then went to board at 181 Jennings Street.

The total population of Zone 1 in 1916 was 215 persons. The three incident cases in this zone give, therefore, an incidence rate of 1.40 per cent. in 1916. Two of these incident cases appeared in the district adjacent to Spartan Mills proper, in which district the population in Zone 1 numbered forty-four persons in 1916, giving an incidence rate of 4.54 per cent. One of the three incident cases, that of Pellagrin 1377 at 134 Colton Street, appeared within the sewered district of Spartan Mills proper. The population of Zone 1 in the mill village proper in 1916 numbered 171* persons, so that the indicated incidence rate in 1916 was here 0.58 per cent.

* This number includes four persons in the family of Pellagrins 437 and 438 at 254 Howard Street. This house, although in the mill village proper, was one of a small group of houses which have never been sewered.

The two incident pellagrins in Zone 2 in 1916 were sisters, Pellagrins 1399 and 1400, aged 11 and 13, respectively. They had lived in the large house at 201 Greene Street since Dec. 22, 1914. This family was not of the usual mill-village class. The children were receiving education and those at work were engaged as telephone operators and clerks. The house was a large one, privately owned, and had been equipped with water supply and sewer before the mill village proper was sewered. The house was not screened. In June, 1916, the two girls developed an initial pellagrous erythema at the same time. The diagnosis of pellagra was made by the family physician and they were admitted as outpatients at the Pellagra Hospital of the U. S. Public Health Service. During September and October, 1915, their aunt, Pellagrin 880, had been at their home on a visit. She had annual attacks of pellagra from 1912 to 1914, inclusive, but has had none since. The interval between her departure and the onset of erythema in the children was more than six months. The house next door, 217 Greene Street, was occupied by active pellagrins in 1915 and also in 1916. This house, 217 Greene Street, was not sewered, but was provided with an outhouse privy, which had been sanitary according to the requirements of the health authorities in 1914. Since then it had gradually become dilapidated. When inspected on Aug. 16, 1916, it was found in a filthy condition. The screen was broken out of the ventilator opening, the hinged drop cover at the back was broken off and excrement openly exposed and covered with flies. The surface of the ground was polluted for a considerable distance at the back of the outhouse. This outhouse was located about 25 yards back of 217 Greene Street and about 30 yards from the unscreened windows of the dining-room and kitchen of 201 Greene Street. Each of these houses had incident cases of pellagra in 1916 and the two at 201 Greene Street, those of Pellagrins 1399 and 1400, fall into the second zone in this study. These are the only incident cases in Zone 2 in 1916, that is, the only new cases of pellagra originating in households previously free from this disease. It would seem that the condition of the privy of the house next door may have had more than accidental relation to these cases.

The population in Zone 2 for the entire community in 1916 numbered 1,006 persons, so that the incidence rate in this zone was 0.20 per cent. For the district adjacent to the mill village proper, the population in Zone 2 numbered 139, so that the two incident cases in this population give an indicated incidence rate of 1.44 per cent. In the mill village proper the population of Zone 2 numbered 867* persons. No incident cases of pellagra were found here.

*This number includes eight persons living in unsewered mill houses at 112 Farley Avenue and 264 Howard Street.

In Zone 3 the population of the entire community numbered 940 persons, of the adjacent district, 146 persons, and of the mill village proper, 794* persons. No incident cases of pellagra could be found in this population in 1916.

COMMENT

In the foregoing pages we have attempted to present in detail the records of all the recognized incident cases of pellagra which have originated in Spartan Mills and the district adjacent, in so far as these records relate to location of domicile and to onset of the disease. The incidence rate of pellagra in each of the zones of exposure is shown for each year in Table 17 and is indicated graphically in Figure 13. In the data previous to 1914 there is shown a somewhat higher inci-

TABLE 17.—THE INCIDENCE OF PELLAGRA IN EACH ZONE IN EACH YEAR

Year	Zone 1			Zone 2			Zone 3		
	In- stances of Expo- sure	Inci- dent Pella- grins	Inci- dence%	In- stances of Expo- sure	Inci- dent Pella- grins	Inci- dence%	In- stances of Expo- sure	Inci- dent Pella- grins	Inci- dence%
1912.....	193	4	2.07	589	4	0.68	700	4	0.57
1913.....	427	15	3.51	1,176	12	1.02	925	6	0.65
1914.....	427	7	1.64	1,144	12	1.05	1,050	1	0.10
1915.....	439	5	1.14	1,174	5	0.43	1,069	0	0.00
1916.....	215	3	1.40	1,006	2	0.20	940	0	0.00
1912 and 1913...	620	19	3.06	1,765	16	0.91	1,625	10	0.62
1914 to 1916, in- clusive.....	1,081	15	1.39	3,324	19	0.57	3,059	1	0.03
1912 to 1916, in- clusive.....	1,701	34	2.00	5,089	35	0.69	4,684	11	0.23

dence of pellagra in Zone 1 than in the other zones, but the records for these years indicate very little difference between the incidence in Zone 2 and that in Zone 3. However, in the records for 1914, 1915 and 1916 the zone relationship, to which we have previously called attention, is very distinct. The first census of this population was made in August and September, 1913, and, in our opinion, the incompleteness of the records previous to that time accounts, to a very large extent, for the number of pellagrins assigned to Zone 3. The figures for the last three years, on the other hand, are much more complete and they show very clearly the tendency for new cases of pellagra to appear almost exclusively in persons living in the same house with a pellagrin or next door to such a house.

* This number includes twenty-six persons living in unsewered mill houses at 503 Arch Street, 116 Farley Avenue, 122 Farley Avenue and 316 Howard Street.

From a study of these data one may get the impression that pellagra never appears in people who have not resided in the same house with or next door to a pellagrin within the previous six months. We certainly recognize, nevertheless, that pellagra may occasionally develop in persons, especially adults, who have been away from pellagra districts even for years. When one remembers the remarkable intervals which sometimes elapse between succeeding attacks of pellagra, discussed in a previous paper ² of this series, it would be surprising if the apparent incubation period of the disease were not also very prolonged in some instances, especially in patients whose actual initial attack was so mild as to have passed unrecognized. The essential and important point in

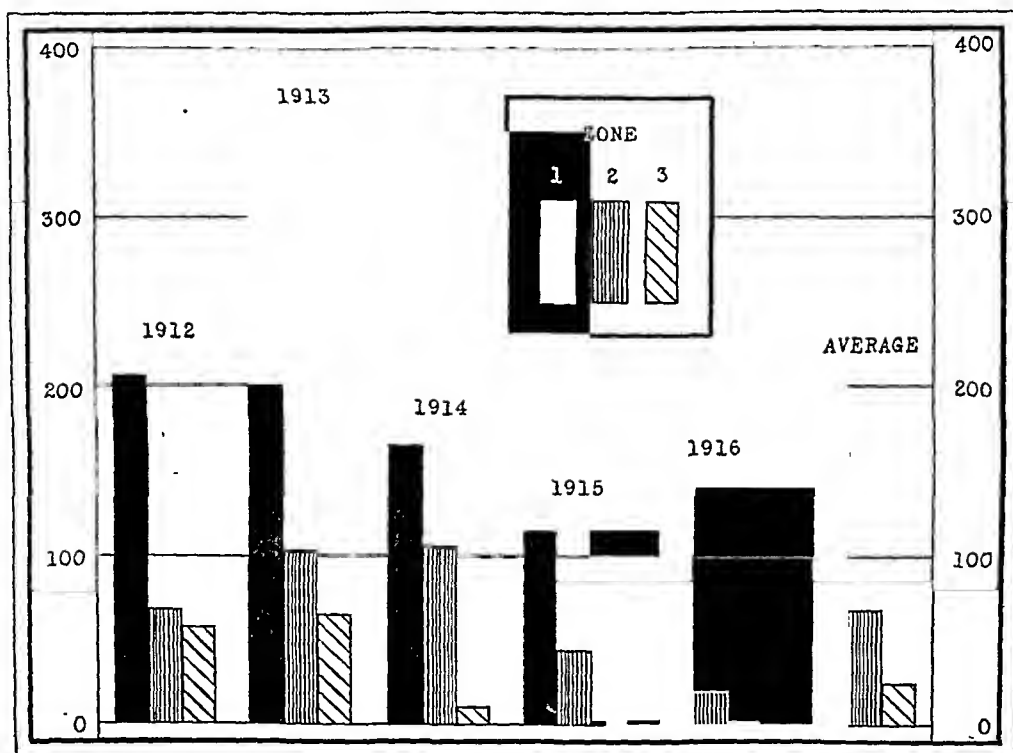


Fig. 13.—Incidence of pellagra per 10,000 population in each of the three domiciliary zones in Spartan Mills and the adjacent district from 1912 to 1916, inclusive. Note the almost complete absence of new cases of pellagra from Zone 3 since the beginning of accurate records at the end of 1913.

this study is that in the active endemic foci of pellagra, where many cases are originating, there the bulk of the new cases appear in persons who have resided very close to active antecedent cases of the disease within the preceding six months and, indeed, within the preceding three months in the warmer season of the year. As indicated in our Second

2. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: The Subsequent History of Pellagrins in Spartanburg County, S. C., Who Survived the Initial Attack. *THE ARCHIVES INT. MED.*, 1916, 18, 340.

Progress Report, we regard this as important evidence that pellagra spreads from preëxisting pellagrins, and that it is ordinarily transmitted to new victims through only very short distances under the conditions obtaining in industrial communities such as this one. It will be noted that since Spartan Mills has been provided with a sewer system, pellagra has shown much less tendency to spread even to the house next door. In 1915 there would appear to be one clear-cut instance of such dissemination from 265 College Street, and in 1916 a similar instance of dissemination from 217 Greene Street. In both instances the relation to defective sanitation was obvious.

Certain criticisms of our previous domicile study have been offered. The actual existence of such a domiciliary relationship has been questioned. The only answer to this criticism we care to offer at present is the suggestion that an analogous complete census and equally complete domicile study be made in other foci of pellagra by those who are not yet convinced. The second criticism has been expressed by Vedder³ in another paper in this present series, constituting our third report. He admits that the zone relationship observed by us may actually exist, but assumes that the real explanation lies in the tendency for people in poor financial circumstances to live near each other in certain sections of these villages, wherein is segregated the population made up of pellagrins and others who consume deficient diets. This assumption would appear not wholly justified in the case of Spartan Mills, for the maps accompanying this paper show that pellagra has been fairly well distributed over the community. Furthermore, we have been unable to discover actual facts in regard to dietary which would support this assumption as far as this community is concerned, nor are we at all convinced that Vedder, in his own observation, was able to discover such facts. This investigator has also assumed that the higher incidence of pellagra in our Zone 1 is just what would be expected if the disease were due essentially to the dietary. A certain confusion of ideas seems to exist in this connection. Our observations do not indicate the frequent simultaneous development of pellagra in several members of a household previously free from the disease and, indeed, such cases have not been assigned to Zone 1. The usual course of events is exemplified by the appearance of one case of pellagra in the household, followed after several months, or even years, by the secondary cases. Such secondary cases have been classed in Zone 1. Vedder has apparently failed to perceive this distinction, or else he has overlooked its significance. Indeed, we have been able to observe, in some instances, that the appearance of one case of pellagra in a family has been followed by definite changes in the

3. Vedder, E. B.: Dietary Deficiency as the Etiological Factor in Pellagra, *THE ARCHIVES INT. MED.*, 1916, **18**, 137.

family dietary, in spite of which subsequent cases of pellagra have appeared in the household in the following years. In this connection it is interesting to note, also, the not uncommon association in the same household of active and inactive cases of pellagra. Such associations may be seen on the map for 1913, Figure 9, at 135 Burnett Street, 128 Colton Street, 254 Howard Street and 115 Wolfe Street. On the map for 1914, Figure 10, similar associations may be seen at 135 Burnett Street, 317 College Street, 135 Choice Street, 111 Jennings Street and 137 Johnson Street. On the maps for 1915 and 1916 such associations are even more numerous. Assuming, as Vedder has, that the members of the household consume the same diet and that the deficiency in this diet may be the cause of pellagra and explain its zone distribution, it is, at least, somewhat curious that one member of the family recovers and in another member the disease recurs while still another member has an initial attack of the disease at the same time, and that such associations of active and inactive pellagrins in the same household are so frequently observed.

In addition to presenting a study of the relation of incident pellagra to domicile, this paper offers also detailed records in regard to the influence on the pellagra situation of the installation of sewers at Spartan Mills, which we have discussed more briefly in the immediately preceding paper of this series. Vedder, in his paper, refers to the installation of sewers at Spartan Mills and suggests that the adherents of the infection theory will be furnished their answers by this experiment. He says, "The diet has remained unchanged so far as known." Further on he says, "It would perhaps be unfair to point to the amount of pellagra in Spartan Mills this year as an evidence of the failure of this sewer system to prevent the disease, since the system has only been in full operation since May of this year." This last statement refers, of course, to 1914. A careful scrutiny of the new cases of pellagra in 1914, with due attention to their residences and the time of onset of the disease, shows at least a suggestive relation to the date of sewer installation in 1913 or 1914. This relationship has become more distinct in the subsequent years, as will be seen by reference to the maps. The total number of incident cases, including the doubtful cases and the total number of other active pellagrins residing in Spartan Mills and in the adjacent surveyed district in each year are shown in Table 18, and the data are presented graphically in Figure 14. It seems to us that the change in pellagra incidence has been rather striking, so definite, in fact, that the supporters of the theory of dietary deficiency might be willing now to assume that a change in diet had taken place. Any such assumption would, obviously, at once lead to a dilemma, because of the large number of nonincident active cases of pellagra present in 1914, 1915 and even in 1916, for whom a poor diet would require to be

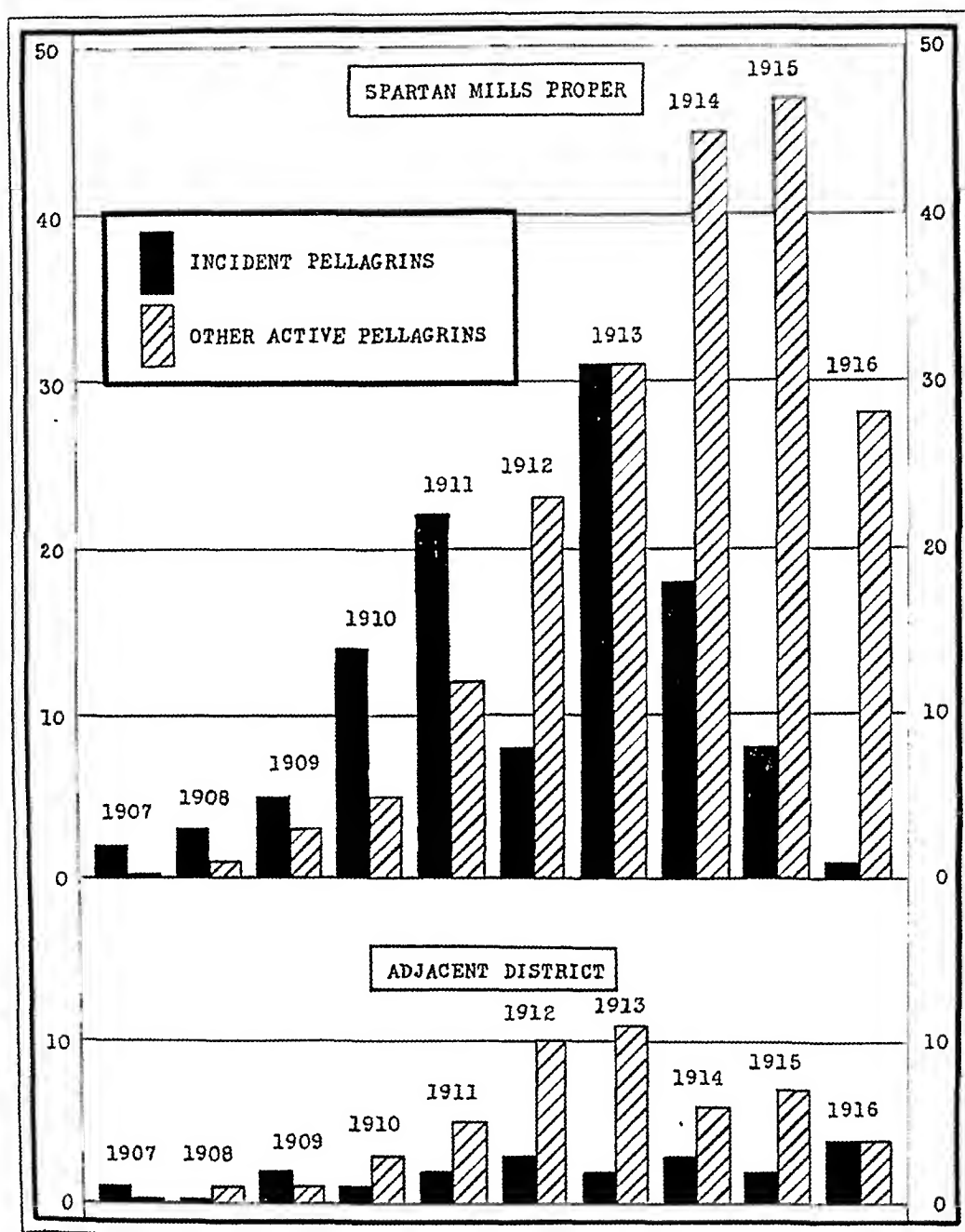


Fig. 14.—The actual number of pellagrins incident in each year and the number of other active pellagrins present in each year in Spartan Mills and the district adjacent to it. The water-carriage system of sewers was installed in Spartan Mills proper, between August, 1913, and May, 1914. Note the very considerable reduction in the number of incident pellagrins in the subsequent years and the absence of a corresponding diminution in the number of other active pellagrins.

assumed. When, in addition, it is recalled that Vedder's observations in the fall of 1914 indicated that the diet had remained unchanged so far as known and that our own observations in 1914, 1915 and 1916 have shown no essential change in the dietary of the general population, but, on the other hand, a very definite addition to the food of the older nonincident cases of the disease in 1915 and 1916, the assumption of a dietary improvement as the cause of the diminished incidence of pel-

TABLE 18.—INCIDENT CASES OF PELLAGRA AND OTHER ACTIVE CASES OF PELLAGRA IN SPARTAN MILLS IN EACH YEAR TO AUG. 1, 1916

	1907	1908	1909	1910	1911	1912	1913	1914	1915	1916
Spartan Mills										
Incident cases.....	2	3	5	14	22	8	31	18	8	1
Other active cases.....	0	1	3	5	12	23	31	45	47	28
Adjacent District										
Incident cases.....	1	0	2	1	2	3	2	3	2	4
Other active cases.....	0	1	1	3	5	10	11	6	7	4

lagra would appear not only useless for the argument, but also opposed to the observed facts.

The domiciliary relationship of newly incident cases of pellagra to old cases of the disease in this community has been found to be quite similar to the relationship demonstrated in our previous study and we are still very strongly of the opinion that this relationship indicates

TABLE 19.—DISTRIBUTION ACCORDING TO SEX AND AGE, OF THE 133 CASES OF PELLAGRA INCIDENT IN SPARTAN MILLS AND ADJACENT DISTRICT FROM 1907 TO 1916, INCLUSIVE

Age	0-14	15-29	30-44	Over 45	Age Unknown	Total
Females.....	22	35	32	12	2	103
Males.....	17	1	4	8	0	30

unmistakably the infectious nature of pellagra, as well as the fact that it spreads only slowly and only through very short distances, as a rule. It is, furthermore, evident that it spreads to only a small part of the exposed population and that the males in the age period from fifteen to forty-five years* are not often susceptible. Of the 133 persons who

* The relative insusceptibility to pellagra of young adult men is generally recognized. If one should desire, therefore, to obtain positive results in experimental inoculations of man, it would obviously be wise to select the experimental subjects from some other group of the population, children from 2 to 10 years of age and childbearing women from 20 to 45 being most valuable for this purpose. The recently published negative experiment carried out by the United States Public Health Service (Goldberger, Joseph: The Trans-

contracted pellagra in Spartan Mills and the district adjacent to it during the ten years 1907 to 1916, inclusive, only five were men in the age period 15 to 45, as will be seen in Table 19. The ages of four of these men were 41, 44, 28 and 36, respectively, and the fifth was a man between 40 and 50. All were factory laborers and one of them is known to have been a chronic alcoholic.

In its tendency to attack only a small part of the exposed population, pellagra would appear to resemble more nearly such relatively noncontagious diseases as leprosy, tuberculosis and typhoid fever, rather than the more actively contagious disorders, such as small-pox, measles or diphtheria.

SUMMARY

1. Spartan Mills is a fairly typical cotton-mill village in which pellagra has long been endemic.

2. The incomplete data for the years previous to 1914 do not permit one to decide whether location of domicile was correlated with incidence of pellagra at that time.

3. Since 1914 nearly all newly incident cases of pellagra in this community developed while the persons were residing in the same house with or next door to a pellagrin in the active stage of the disease, or within six months after the termination of such exposure.

4. Since the installation of the sewer system, the spread of pellagra has been decidedly restricted. In 1916 the only considerable focus of new cases was in the immediate neighborhood of a dilapidated out-house privy used by pellagrins.

5. The present more detailed study of more complete data in regard to this community shows the relation of domicile to pellagra here to be essentially similar to the relation shown by the other five villages reported on in our Second Progress Report. At the time of that report, the apparent relationship in this one village was exceptional.

6. These studies support our previous conclusion that pellagra is an infectious disease, which spreads slowly, attacking only a small proportion of the population residing in the immediate vicinity, and they indicate, further, that its spread is especially favored by insanitary methods for the disposal of human wastes.

missibility of Pellagra, *Pub. Health Rep.*, 1916, **31**, 3159) would appear, therefore, to have little or no bearing on the question of the transmissibility of pellagra, although it may be of some value in confirming the previously well known fact that healthy men in the more active period of life are quite refractory to the disease.

TABLE 20.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1912

1912	Zone 1					Zone 2			Zone 3			
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
Allen	No data for 1912	415	Entire 1912.....	3	0			
115	Entire 1912.....	3	0	445, 16, 505, 506	Entire 1912.....	2	0			
117	445	1907	Entire 1912.....	3	0
118
121
127	...	1908	Early 1912 to end 1912...	9	0	Entire 1912.....	3	0
128	16	1912	Oct. to end 1912
	505	1912	505, 506, 16	Entire 1912.....	4	0	Entire 1912.....	7	0
130	506	1912	Entire 1912.....	3	0
131	Entire 1912.....	5	0
137	Entire 1912.....	7	0
141	No data for 1912	Entire 1912.....	7	0
145	16, 505, 506	Entire 1912.....	6	0	Entire 1912.....	7	0
148	Entire 1912.....	7	0
148	Entire 1912.....	7	0
149	Entire 1912.....	7	0
Arch	Entire 1912.....	7	0
371	64	1910	To March, 1912. (No	Entire 1912.....	9	0
	65	1910	other members of	235, 64, 65	Entire 1912.....	8	0	Entire 1912.....	9	0
370	family. No further	To Spring, 1912.....	7	0	Spring to end 1912.....	7	0
385	data for 1912)	105
393
397	105	1911	To Spring, 1912. (No
	other members of
	family. No further
	data for 1912)
403	105	To Spring, 1912.....	9	0	Spring to end 1912.....	9	0
409	Entire 1912.....	12	0
503
Bravley
190	No data for 1912
191
194
195	No data for 1912	Entire 1912.....	6	0
196	Dec. to end 1912.....	5	0
197	202	1912	Aug. 1 to Aug. 28, 1912	5	0	(No data to Dec.)
	(Moved Aug. 28)	Entire 1912.....	9	0
201
202	To Aug. 1, 1912.....	6	1
202	Aug. 28 to end 1912.....	7	0
204	(New family Aug. 28)
205	202	Aug. 1 to Aug. 28,	5	0	Sept. to end 1912.....	7	0
218	202	1912	6	0	(No data to Sept.)	5	0
219	No data for 1912	202	Aug. 1 to Aug. 28,	2	0	Aug. 28 to end 1912	6	0
	1912	To Aug., 1912.....	2	0
224	Aug. 28 to end 1912	3	0
	445	Entire 1912.....	6	0	Sept. to end 1912.....	3	0
	(No data to Sept.)

[illegible]

TABLE 20.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1912—(Continued)

1912	Zone 1				Zone 2				Zone 3				
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
					Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
174	443	Aug. to end 1912..... (No data to Aug.)	6	0
175	Entire 1912.....	3	0
181	Entire 1912.....	5	0
182	No data for 1912
Chole-	206	Entire 1912.....	4	0
111	...	206	1911	Entire 1912.....	4	0	203, 204, 515, 206	Entire 1912.....	3	0
119
127
135	No data for 1912
224	See 134-142 Montgom- ery St.
College
151-155	Entire 1912.....	4	0
163-167	Entire 1912.....	14	0
178	Entire 1912.....	3	0
176-179	Entire 1912.....	6	0
186	No data for 1912
191	No data for 1912
194	...	105	1911	Spring to end 1912..... (No data to Spring)	18	0
254	Oct. to end 1912..... (No data to Oct.)	4	0
260	Entire 1912.....	5	0
264	238	Entire 1912.....	7	0
265	No data for 1912
271	Aug. to end 1912..... (No data to Aug.)	7	0
272
277	238	Oct. to end 1912..... (No data to Oct.)	7	0
278	Entire 1912.....	3	0
282	203, 204	To Feb., 1912.....	4	0	Feb. to end 1912.....	4	0
283	No data for 1912
283	No data for 1912
291	See 283 Brawley
294	See 296 Brawley
297
298	236	To Aug., 1912.....	5	0	Aug. to end 1912.....	5	0
303	236	To Aug., 1912.....	2	0	Aug. to end 1912.....	2	0
304	Entire 1912.....	4	0
310	No data for 1912	Entire 1912.....	6	0
311	197	June to end 1912.....	5	0	To June, 1912.....	5	0
317	...	197	1912	June to end 1912.....	17	0	...	June to Aug., 1912..... (Moved Aug. No further data for 1912)	5	1	To June, 1912..... To June, 1912..... Mar. to June, 1912..... (No data to Mar.)	14	1
325	197	...	5	0	...	5	0
331	June to end 1912..... (No data to June)	5	0
334	194, 70	Mar. to end 1912..... (No data to Mar.)	3	0

327 328 343	1911 1912	198 328	328, 198	Entire 1912	4	0	0	0
344	625 626	1911 1912	328, 198, 625, 626	Entire 1912	6	0	0	0
Colton 100 110	1911 1912	1907 1912	1313	Fall to end 1912	6	0	0	0
116 119	444* 1313	1907 1912	1313, 237	Entire 1912	4	0	0	0
122	1908	1912	1313, 33, 237	Entire 1912	2	0	0	0
127	1912	1912	237	Entire 1912	2	0	0	0
128	1912	1912	443	Apr. to end 1912 (No data to Apr.)	2	0	0	0
131	1912	1912	443	June to end 1912	5	0	0	0
134	1912	1912	203, 204	Entire 1912	9	0	0	0
135	1912	1912	515, 206	Entire 1912	3	0	0	0
138	1912	1912	232	Entire 1912	5	0	0	0
142	1912	1912	232	Oct. to end 1912 (No data to Oct.)	6	0	0	0
148	1912	1912	105	To Spring, 1912	6	0	0	0
156	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
Dickson 116 118	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
120	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
126	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
128	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
130	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
132	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
134	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
Duncan 103 104 113 114	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
121	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
122	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
129	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
130	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
137	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0
138	1912	1912	105	Spring to end 1912 (No further data for 1912)	6	0	0	0

TABLE 20.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1912—(Continued)

1912	Zone 1				Zone 2				Zone 3			
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
115	No data for 1912	235	Nov. to end 1912..... (No data to Nov.)	7	0			
116			
153	235	1911	No data for 1912	6	0	436, 437	Oct. to end 1912.....	2	0	To Oct., 1912.....	2	0
154	Entire 1912.....	113, 115	Entire 1912.....	2	0	Entire 1912.....	7	0
Farley			
112			
116.			
122	115	1909	Entire 1912.....	1	0			
133	113	1912	Sept. to end 1912.....	6	1	113, 115, 503	To Oct., 1912.....	6	0			
111	503	1911	Oct. to Nov. 29, 1912..... (Family of Case 503 counted at 118 Man- ning for 1912)			
147	No data for 1912	503	Oct. to end 1912.....	8	0	To Oct., 1912.....	8	0
148	503	Entire 1912.....	3	0	Entire 1912.....	8	0
153			
154			
150			
160	No data for 1912			
166	893	1912	No data for 1912	7	0	To Summer, 1912.....	8	1
171	Summer to end 1912.....			
172	No data for 1912			
177	No data for 1912			
178	No data for 1912			
189	No data for 1912			
190	See 360 Brawley			
203	68, 69	Entire 1912.....	4	0			
213	68, 69, 232	Entire 1912.....	7	0			
214	Entire 1912.....	5	0
221	232	Entire 1912.....	6	0			
222	750	Aug. to end 1912.....	5	0	To Aug., 1912.....	5	0
229	750	1910	Aug. to end 1912.....	1	0	750	Aug. to end 1912.....	7	0	To Aug., 1912.....	7	0
230	(No data to Aug.)			
237	No data for 1912	748, 750, 574	Entire 1912.....	6	0			
238			
245	No data for 1912			
246	No data for 1912	3	0			
253	574	1911	Entire 1912.....			
254	No data for 1912	574	Sept. to end 1912..... (No data to Sept.)	7	0			
Forest	Entire 1912.....	3	0
272	No data for 1912			
276	No data for 1912			
304	No data for 1912	To June, 1912.....	12	0
365	197	June to end 1912.....	12	0			

316</
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-------

TABLE 20.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1912—(Continued)

1912	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
House Street and Number										
222	Entire 1912.....
230	Entire 1912.....
236	435	1910	5	0	Entire 1912.....
254	436	1910	Oct. to end 1912..... (No data to Oct.)					
261	437	1910	436, 437	Oct. to end 1912.....	4	0	To Oct., 1912.....
316	Entire 1912.....
Jennings	
110	207	1907	Entire 1912.....	3	0	207	Entire 1912.....	2	0	
111	207, 1290, 1291, 1292	Entire 1912.....	2	0	
118	
119	No data for 1912	1290, 63, 1291, 64, 1292, 65	Entire 1912.....	3	0	
126	
127	No data for 1912	
134	No data for 1912	
135	No data for 1912	
142	No data for 1912	
143	No data for 1912	
150	No data for 1912	
151	Entire 1912.....
153	Entire 1912.....
159	No data for 1912	
165	No data for 1912	
167	
174	508	Mar. to May, 1912.....	5	0	To Mar., 1912.....
175	508	1911	Mar. to May, 1912.....	5	0	508	Mar. to May, 1912.....	3	0	May to end 1912
181	To Mar., 1912.....
182	No data for 1912	May to end 1912
Johnson	508	Mar. to May, 1912.....	5	0	To Mar., 1912.....
111	May to end 1912
112	11	To Sept., 1912.....	5	0	To Mar., 1912.....
116	11	1910	To Sept., 1912..... (Moved Sept.)	4	0	11	Aug. to Sept., 1912..... (No data to Aug.)	5	0	May to end 1912
117	Sept. to end 1912.....
123	11	To Sept., 1912.....	3	0	Sept. to end 1912.....
127	11	To Sept., 1912.....	3	0	Sept. to end 1912.....
128	116, 105	Entire 1912.....	7	0	Sept. to end 1912.....
131	No data for 1912	
137	116	1909	Entire 1912.....	2	0	116	Entire 1912.....	2	0	

[illegible]

TABLE 20.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1912—(Continued)

1912	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
House Street and Number										
153	Entire 1912.....
158	Entire 1912.....
159	Aug. to end 1912.....
165	(No data to Aug.)
166	Entire 1912.....
Montgomery										Entire 1912.....
134	(Tenement house)
138	Entire 1912.....
142	Entire 1912.....
350	
Oliver										
113	749	1910	195	Entire 1912.....	7	0	
114	70, 194, 195	Entire 1912.....	2	0	
119	750	Aug. to end 1912.....	2	0	
120	Aug. to end 1912.....	8	0	
127	750	To Aug., 1912.....
128	Entire 1912.....
135	748, 750	Entire 1912.....	4	0	
136	748, 625,	Entire 1912.....	3	0	
	626	
141	748	1911	Entire 1912.....	4	0	
142	748, 625,	Entire 1912.....	6	0	
	626	
Vaughn										
1	Entire 1912.....
2	No data for 1912	Entire 1912.....
3	
Wolfe										
111	
112	No data for 1912	
114	33	1910	June to end 1912.....	4	0	33, 25, 26,	Entire 1912.....	5	0	
	(No data to June)	27, 1313	
115	25	1910	Entire 1912.....	4	2	
	26	...	June to end 1912	
120	27	1912	
	1313	1912	Spring to Fall, 1912.....	1	0	237, 25	To Spring, 1912.....	2	1	
	(Moved fall)	
121	25, 26, 27,	Entire 1912.....	5	0	
	33, 1313	
132	1313	Spring to Fall, 1912... (No further data for 1912)	5	0	

TABLE 21.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1913

1913	Zone 1										Zone 2		Zone 3	
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population		
					Total	Incident Cases			Total	Incident Cases		Total	Incident Cases	
Allen	115	No data for 1913	445, 46, 60, 61, 740	To Dec., 1913.....	4	0	Dec. to end 1913.....	4	0	
117	1907	To Oct., 1913.....	3	0	
118	445	1912	1912	Oct. to Dec., 1913 (New family Oct. counted at 217 Greene)	445, 46, 60, 61, 740	To Dec., 1913.....	2	0	Dec. to end 1913.....	2	0	
124	860*	1912	1912	To Aug., 1913 (Moved Aug.)	9	0	445, 46, 60, 61	Sept. to end 1913 (New family Sept.)	3	0	To Feb., 1913.....	3	1	
127	740	1913	1913	Feb. to Oct., 1913. (Moved Oct.; no fur- ther data)	2	0	
128	16	1908	1908	To Mar., 1913 (Moved Mar.)	16, 505, 506 740	To Aug., 1913.....	4	0	Aug. to end 1913. To Feb., 1913.....	4	0	
130	305	1912	1912	Nov. to end 1913 (No data to Nov.; family counted at 118 Allen for 1913)	
131	506	1912	1912	Sept. to end 1913 (No data to Sept.)	5	0	16, 505, 506, 445	Entire 1913.....	10	0	Entire 1913.....	5	0	
137	
141	445	1907	1907	
145	
148	
149	
Arch	371	
379	...	1913	1913	
385	
393	
397	
403	
409	
503	
Brawley	190	
191	
194	
195	
196	
197	
201	
202	

1913	Zone 1					Zone 2			Zone 3		
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
					Total	Incident Cases			Total	Incident Cases	
204	Entire 1913.....
205	Mar. to end 1913.....
218	(No data to Mar.)
219	Entire 1913.....
221	445, 46, 60, 61	To Dec., 1913.....	6	0	Entire 1913.....
225	445, 46, 60, 61	To Dec., 1913.....	3	0	Dec. to end 1913.....
230	Entire 1913.....
231	Dec. to end 1913.....
234	445, 16, 505, 506 236, 238	Entire 1913.....	3	0	Apr. to end 1913.....
235	To June, 1913.....	6	0	(No data to Apr.)
248	16, 445, 505, 506 445	Sept. to Nov., 1913	5	0	June to Sept., 1913.....
256	Entire 1913.....	4	0	Nov. to end 1913
272	236, 1134	To June, 1913.....	6	0	June to Nov., 1913.....
280	Sept. to Nov., 1913	4	0	(No data to June)
288	Entire 1913.....	7	0	Aug. to end 1913.....
296	Nov. to end 1913.....	6	0	Apr. to end 1913.....
302	To Aug., 1913.....	15	0	(No data to Apr.)
303	May to end 1913.....
306	(No data to May)
309	June to end 1913.....
312	(No data to June)
316	Entire 1913.....
324	Mar. to end 1913.....
334	1016	June to July, 1913.....	9	0	(No data to Mar.)
339	...	1016	1913	June 15 to July, 1913... (Moved July)	10	0	238, 1016 68, 238	Entire 1913.....	6	0	Entire 1913.....
342	To June 15, 1913.....	5	0	Mar. to end 1913.....
350	68, 69, 238, 1016	July to end 1913 (New family)	2	0	Entire 1913.....
360	68, 69, 238	Entire 1913.....	6	0	Entire 1913.....
384	May to end 1913.....	10	0	(No data to May)
389	Entire 1913.....
390	232	Entire 1913.....	8	0	Entire 1913.....
396	232	Entire 1913.....	4	0	Entire 1913.....
402	Entire 1913.....
Burnett	Entire 1913.....
109	Entire 1913.....
110	Entire 1913.....

[illegible]

1913	Zone 1				Zone 2			Zone 3		
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population	
					Total	Incident Cases			Total	Incident Cases
254 (cont'd)	1010	1913		July to Oct., 1913 (New family; count- ed at 342 Braw- ley; no further data)	796, 987, 1016	May to end 1913.....	8	0
260	238, 738, 987	Entire 1913.....	7	0
261	738	Aug. to Fall, 1913..... (No data to Aug.; moved Fall)	5	0
265	987	1909		Dec. to end 1913..... (New family)	7	0	738, 987	June to end 1913.....	7	0
271	238	To May, 1913.....	7	1
272	738	1913		June to end 1913.....	6	0	738	June to end 1913.....	3	0
277	738	To June, 1913.....	4	0
278	738	To June, 1913.....	7	0
282	Entire 1913.....	6	0
283
291
294
297	94, 548, 1134	June to end 1913.....	6	0
298	94	Nov. to end 1913.....	6	0
303	548, 94	June to end 1913.....	4	0
304	94	1909		Nov. to end 1913..... (Family of Case 94 not counted here for 1913)	6	0
310	197, 989, 94	June to end 1913..... (No data to June)	7	0
311	197, 989, 94	Entire 1913.....	5	0
317	197	1912		Entire 1913.....	13	1
325	989	1913		June to end 1913.....	194, 70, 739, 796	Entire 1913.....	7	0
331	No data for 1913.....	5	1	198, 828, 739, 796	Entire 1913.....	6	0
334	796	1913		July to end 1913..... (Family of Case 796 counted at 254 Col- lege)	198, 328	Mar. to June, 1913..... (No data to Mar.)	10	1
337	Aug. 15 to Nov., 1913.. (New family; mov- ed Nov.)	8	0
338	739	1913		June to Aug., 1913..... (Moved Aug.)	9	0	Dec. to end 1913 (New family; counted at 116 Colton)
343	444	1907	
	198	1911		Entire 1913.....	5	0

[illegible]

TABLE 21—DOMICILE RELATIONSHIP—SPARTAN MILLS—1913—(Continued)

House Street and Number	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
Duncan 103	1170	1912	Mar. to May, 1913..... (No data to Mar.; moved May)	3	0	232	May to end 1913..... (New family)	4	0	
104	232, 1170	Mar. to end 1913..... (No data to Mar.)	4	0	
113	June to end 1913..... (No data to June)
114	1170	Mar. to May, 1913.....	6	0	May to end 1913.....
121	Entire 1913.....
122	Entire 1913.....
129	Entire 1913.....
130	Entire 1913.....
137	515	Sept. to end 1913.....	4	0	Entire 1913.....
138	515	Sept. to end 1913..... (No data to Sept.)	3	0	To Sept., 1913.....
145	515	1910	Sept. to end 1913..... (New family; count- ed at 132 Diekson)	235, 583	To Sept., 1913..... (Moved Sept.)	8	0	
146	235, 515	Entire 1913.....	13	0	
153	235, 515, 583	June to end 1913..... (No data to June)	5	0	
154	235	1911	Entire 1913.....	13	0	436, 437, 438	Entire 1913.....	2	0	
Farley 112	113, 115	Entire 1913.....	Entire 1913.....
116	
122	115	1909	Entire 1913.....	4	0	2	0	
133	113	1912	To Feb., 1913 (Moved Feb.)	
141	1014	1913	Spring to end 1913.....	6	0	1014, 1358	June to end 1913..... (No data to June)	13	0	
147	Apr. to end 1913.....	4	0	To Mar., 1913..... (Moved Mar.)
148	1011	(New family)	To Nov., 1913.....
153	1358	Nov. to end 1913.....	3	0	Mar. to end 1913.....
154	Mar. to end 1913..... (No data to Mar.)
159	893	To Sept., 1913.....	4	0	Sept. to end 1913.....
160	893	June to Sept., 1913..... (No data to June; moved Sept.; no further data)	10	0	
166	893	1912	To Sept., 1913..... (Moved Sept.)	7	0	Sept. to end 1913..... (New family)
171	No data for 1913	238	Sept. to end 1913..... (No data to Sept.)	13	0	
172	
177	238	1911	May to end 1913 (No data to May; family counted at 119 Manning)	

[illegible]

TABLE 21.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1913—(Continued)

House Street and Number	Zone 1						Zone 2			Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
111	936	1913	Sept. to Nov. 25, 1913... (Moved Nov.; family of Case 936 not counted here for 1913)	9	0	236	To June, 1913.....	9	0	June to Sept., 1913.....	9	0
118	236, 936	To June, 1913.....	11	0	June to Sept., 1913.....	11	0
119	236	1911	To June, 1913..... (Moved June)	5	0	536	Sept. to Nov. 25, 1913. Sept. to Nov. 25, 1913.	8	0	June to Sept., 1913... (New family) Nov. 25 to end 1913	8	0
136	See 272 Brawley June to Aug., 1913.....	8	0	To June, 1913.....	9	1
146	1134	1913	(Moved Aug.)	7	0	Aug. to end 1913.....	8	1
154	548	1913	June to Oct., 1913..... (Moved Oct.)	To June, 1913..... Fall to end 1913 (New family)	3	0
162	248	June to Oct., 1913.....	5	0	To June, 1913.....	6	0
172	445, 197, 989	Entire 1913.....	20	0	Oct. to end 1913
181	445	1907	Oct. to Nov. 27, 1913 (Family counted at 118 Allen; no fur- ther data for 1913)	July to end 1913.....	7	0	To July, 1913.....	7	0
181	See 305 Forest	16, 736, 46, 60, 61	Apr. to end 1913..... (No data to Apr.)	4	0
196	See 304 Forest	1	0	328, 198, 46, 60, 61, 796
201	No data for 1913	Entire 1913.....	4	0
206	198, 328, 46, 60, 61	Entire 1913.....
216	105, 590	Entire 1913.....	8	0
217	46	1912	Aug. to Oct., 1913..... (No data to Aug.; moved Oct.; no further data)	105	To Summer, 1913.....	7	1
217	60	1912	13	0	590	Aug. to end 1913..... (No data to Aug.)	6	0
217	61	1912	1419	Entire 1913.....	5	0
226	860	1910	Entire 1913.....	Entire 1913.....	6	0
Howard	1419	Entire 1913.....	5	0	Entire 1913.....	4	0
187	Summer to end 1913.....	Entire 1913.....	11	0
193	530	1913	Entire 1913.....	Entire 1913.....	7	0
199	Entire 1913.....	Entire 1913.....
204	Entire 1913.....	Entire 1913.....
205	Entire 1913.....	Entire 1913.....
212	1419	1912	Entire 1913.....	4	0	..	Entire 1913.....	Entire 1913.....
218	Entire 1913.....	Entire 1913.....
222	Entire 1913.....	Entire 1913.....
230	Entire 1913.....	Entire 1913.....
236	Entire 1913.....	Entire 1913.....
254	436	1910	Entire 1913.....	5	1	..	Entire 1913.....	Entire 1913.....
	437	1910	Entire 1913.....	Entire 1913.....

[illegible]

TABLE 21—DOMICILE RELATIONSHIP—SPARTAN MILLS—1913—(Continued)

1913	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
122	434	Mar. to July, 1913.....	3	0	To Mar., 1913.....
123	434	1912	Mar. to July, 1913..... (New family Mar.; moved July)	12	0	July to end 1913
127	105, 434	To Sept. 1913.....	7	0	To Mar., 1913.....
128	116, 552	Aug. to end 1913..... (No data to Aug.)	3	0	July to end 1913
131 (New house)	Family counted at 353 Forest	116, 552	Entire 1913.....	2	0	Sept. to end 1913.....
131	651, 652, 653, 654,	Entire 1913.....	2	0
137	116 552	1909 1913	Entire 1913..... June to end 1913	3	1	116, 552	Entire 1913.....	2	0
140	105, 590, 116, 552	Entire 1913.....	6	0
141	651, 652, 653, 654	To Oct., 1913..... (Moved Oct.)	6	0
146	651 652 653 654	1913 1913 1913 1910	Oct. 29 to Dec., 1913..... (New family; count- ed at 147 Milan for 1913; no further data)	651, 652, 653, 654, 590	Summer to end 1913...	5	0	To Summer, 1913.....
147
178 Langford	No data for 1913
1	No data for 1913	740	Feb. to Oct., 1913.....	1	0	Entire 1913.....
2	No data for 1913	To Feb., 1913.....
3	No data for 1913	Oct. to end 1913
4	No data for 1913
5	1376, 413, 328, 808	Entire 1913.....	7	0
Laurens	328	1912	Apr. 26 to end 1913..... (No data to Apr.)	4	0	238, 115, 113, 1014, 1358	Entire 1913.....	3	0
153	238, 1358	To May, 1913.....	9	0	May to Nov., 1913.....
159	238, 1014	Nov. to end 1913	5	0
Manning	To Nov., 1913..... (Moved Nov.)	5	0
110
111
118	1358	1913	Nov. to end 1913..... (New family)	11	0

TABLE 21—DOMICILE RELATIONSHIP—SPARTAN MILLS—1913—(Continued)

House Street and Number	Zone 1				Zone 2				Zone 3			
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
1913												
380	718	May to Fall, 1913....	5	0	To May, 1913..... Fall to end 1913	5	0
Oliver												
113	749	1910	901	Dec. to end 1913.....	7	0	To Dec., 1913.....	7	0
114	828	1911	739, 191, 70	Entire 1913.....	2	0			
110	625	1911	750, 904	Entire 1913.....	6	0			
120	739	June to Aug., 1913....	7	0	To June, 1913..... Aug. to end 1913	7	0
127	750	Entire 1913.....	8	0			
128	739	June to Aug., 1913....	6	0	To June, 1913.....	6	0
135	747, 748,	Entire 1913.....	4	0			
136	750	Entire 1913.....	3	0			
141	748	1911	...	4	0	747, 748	To Aug., 1913.....	7	1			
142	747	1913	...	6	0	748	Feb. to end 1913.....	8	0	To Feb., 1913.....	8	0
Vaughn												
1	510, 511, 512, 737, 1223, 651, 652, 653, 654	Feb. to end 1913.....	7	0			
2	511	1911	Feb. to end 1913..... (No data to Feb.)	7	3							
	510	1913	Apr. to end 1913									
	512	1913	May to end 1913									
	737	1913	Sept. to end 1913									
3	510, 511, 512, 737, 651, 652, 653, 654	Feb. to end 1913.....	7	0	To Feb., 1913.....	7	0
Wolfe												
111	25, 26, 27, 33	Feb. to Oct., 1913.... (No data to Feb.)	8	0	Oct. to end 1913.....	8	0
112	25, 26, 27, 33, 1313	Entire 1913.....	5	0			
114	33	1910	To Aug., 1913..... (Moved Aug.)	4	0	25, 26, 27, 1313, 237	Aug. to end 1913..... (New family)	9	0			
115	25	1910	To Oct., 1913..... (Moved Oct.)	2	0	Dec. to end 1913..... (New family)	5	0
	26	1912	...									
	27	1912	...									
120	237, 323, 25, 26, 27, 33	May to end 1913..... (No data to May)	3	0			
121	25, 26, 27, 33	To Oct., 1913.....	5	0	Oct. to end 1913.....	5	0
132	328	May to end 1913..... (No data to May)	4	0			

	Zone 3
MILLS--1914	

[illegible]

TABLE 22.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1914—(Continued)

1914	Zone 1				Zone 2			Zone 3					
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
					Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
218	Entire 1914.....	2	0
219	Entire 1914.....	3	0
221	Entire 1914.....	6	0
225	Entire 1914.....	4	0
230	Entire 1914.....	3	0
231	Entire 1914.....	8	0
234	3	0	Entire 1914.....	6	0
235	5	0	Entire 1914.....	7	0
248	4	0	To Dec., 1914.....	19	0
250	3	0	May to end 1914.....	6	0
272	(No data to May)	5	0
280	6	0	To Summer, 1914.....	6	0
283	To Mar., 1914.....	4	0
296	2	0	To Mar., 1914.....	2	0
302	1421	1913	...	Summer to end 1914..... (No data to June)	11	0	1421	Summer to end 1914.....	6	0	Sept. to end 1914.....	5	0
303	Mar. to Apr., 1914.....	13	0	1421, 55	Mar. to end 1914.....	5	0	(New family)	5	0
306	55	1912	...	(New family Mar., moved Apr.)	1421, 493	June to end 1914.....	6	0	To June, 1914.....	8	0
309	1421, 493, 55	Mar. to end 1914.....	4	0	Aug. to end 1914	12	0
312	493	1913	...	June to Aug., 1914..... (Moved Aug.)	4	0	55	Mar. to Apr., 1914.....	2	0	Entire 1914.....	7	0
316	June to Aug., 1914.....	5	0	Entire 1914.....	3	0
321	Entire 1914.....	4	0
334	3	0	To Summer, 1914.....	10	0
339	1269	June to end 1914.....	To May, 1914.....	4	0
342	June to end 1914.....
350	68	(No data to June)	6	0
360	68, 69, 1295	Entire 1914.....	11	0
384	Feb. to end 1914.....	16	0
389	68, 69, 1295	(No data to Feb.)
390	Entire 1914.....
396
402
Burnett
109	1290, 1291	Summer to end 1914.....	3	0	To Summer, 1914.....	3	0
110	May to end 1914.....	3	0	Entire 1914.....	10	0
117	1290, 1291, 555	Entire 1914.....	5	0	To May, 1914.....	4	0
118	444, 913, 939, 1309, 555	Entire 1914.....	5	0
127	555	1911	...	May to end 1914..... (New family)	5	0	64	To Apr., 1914..... (Moved Apr.)	5	0
128	Family counted at 122 Colton for 1914

134	Family counted at 149 Allen for 1914	1	0	Entire 1914.....	1	0	
135	64	1910	Entire 1914.....	1337, 742, 64, 198, 1305	2	0	
144	65*	1910	...	5	0	1305, 1310, 1337, 736, 703, 198, 742	6	0	
145	1337	1913	Entire 1914.....	1337, 736, 703, 198, 742	2	0	
152	198	1911	Nov. to end 1914..... (Family counted at 160 Burnett for 1914)	4	0	1337, 736, 703, 198, 736, 703, 1310, 742	10	0	
153	Apr. to Nov., 1914..... (New family; moved Nov.; no further data for 1914)	6	0	1312, 1026, 703, 736, 198	3	0	
160	198	1911	Entire 1914.....	1312, 1026, 1310, 736, 703, 1376, 912, 868, 198	11	0	
161	703	1912	912, 1312, 1026, 868, 1376	10	0	
167	736	1913	...	2	1	Entire 1914.....	6	0	
168	Entire 1914.....	8	0	
174	Entire 1914.....	4	0	
175	1312	1913	Entire 1914.....	Entire 1914.....	2	0	
181	1026	1914	July 23 to Sept., 1914 (Moved Sept.)	Entire 1914.....	3	0	
182	Entire 1914.....	7	0	
Choice	Entire 1914.....	6	0	
111	206	1911	To Apr., 1914..... (Moved Apr.)	4	0	To Fall, 1914..... Apr. to end 1914..... (New family)	4	0	
119	Entire 1914.....	3	0	
127	3	1	Fall to end 1914..... (New family)	6	0	
135	651	1913	To Fall, 1914..... (Moved fall)	Entire 1914.....	4	0	
224	652	1913	Entire 1914.....	14	0	
College	653	1913	Entire 1914.....	3	0	
151-155	654	1914	June to Fall, 1914 (See 134-142 Montgomery)	Entire 1914.....	6	0	
163-167	1005	Entire 1914.....	6	0	
178	Entire 1914.....	6	0	
175-179	Entire 1914.....	6	0	
186	Aug. to end 1914..... (No data to Aug.)	6	0	
191	

334	444, 706, 1267, 1259, 977	Entire 1914.....	8	0	
337	444, 198, 1060, 1267, 726, 798	Entire 1914.....	7	0	
338	444	1907	To Mar., 1914..... (Moved Mar.; count- ed at 116 Colton for 1914)	198, 726, 1060, 1259, 977	Mar. to end 1914..... (New family)	10	0	
343	198	1911	To Apr., 1914..... (Moved Apr.; count- ed at 160 Burnett for 1914)	1060, 726, 893	Apr. to Fall, 1914..... (New family; mov- ed fall; no fur- ther data for 1914)	4	0	
344	726	1911	To Feb., 1914..... (Moved Feb.; count- ed at 237 Farley for 1914)	747, 893	July to end 1914..... (New family)	9	0	
347	1060	1913	Apr. to July, 1914..... (New family; moved July)	6	0					
348	893	1912	June to end 1914..... (No data to June)	7	0					
	198, 726, 747	To Feb. 15, 1914..... (Moved Feb.; no further data for 1914)	7	4	
Colton	5	0	4
100	444, 913, 939, 1313, 1309	Entire 1914.....	5	0	0
110					
116	444	1907	Mar. to end 1914..... (No data to Mar.)	8	3					
	913	1914	Summer to end 1914							
	939	1914							
	1309	1914	Entire 1914.....	1	0					
119	1313	1912	1313, 444, 939, 913, 1309, 237, 742	Entire 1914.....	11	0	
122					
127	1389	1914	Summer to end 1914.....	1	0		To Summer, 1914.....	2	1	
128	1305	1914	Summer to end 1914.....	6	0		Feb. to Summer, 1914 (No data to Feb.)	7	1	
131	237	1809	Entire 1914.....	3	0					
131	742	1913	Entire 1914.....	2	0		May to end 1914..... (No data to May)	8	0	
135	237, 328, 940, 742, 1310, 1305				
138	1310	1914	Summer to end 1914.....	3	0	198, 328, 742, 940	To Summer, 1914.....	4	1	
142	443	1912	1376, 868, 912, 328, 1310, 940	Entire 1914.....	8	0	
148	868	1913	Entire 1914.....	15	1					
	1376	1913	To Summer, 1914							
	912	1914	Spring to end 1914							

TABLE 22.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1914—(Continued)

1911	Zone 1				Zone 2			Zone 3		
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Time in Zone 2	Exposed Population		Time in Zone 3
					Total	Incident Cases		Total	Incident Cases	
				No data for 1914	Entire 1914.....
	156 Dickson	Feb. to end 1914.....
	116	To death, Feb., 1914..	9	0	..	3	0	May to end 1914.....
	118	1913	...	(Family moved Feb.)	(New family)
	120	1928	3	0	Apr. to end 1914.....
	126	3	0	
	128	3	0	
	130	203	1911	Entire 1914.....	4	0	
	132	204	1911	Entire 1914.....	2	0	..	6	0	
	131	194	1910	
	Duncan	
	103	Entire 1914.....
	114	4	0	Fall to end 1914.....
	113	Entire 1914.....
	114	3	0	To Mar., 1914.....
	121	3	0	Fall to end 1914
	122	3	0	To May, 1914.....
	129	7	0	To Aug., 1914.....
	130	8	0	Oct. to end 1914
	137	9	0	To Aug., 1914.....
	138	8	0	Oct. to end 1914
	145	515	1910	Entire 1914.....	5	0	..	5	0	
	146	8	0	
	153	1283	1912	Nov. to end 1914..	5	0	..	14	0	
	151	235	1911	(New family)	19	0	
	Farley	10	0	
	112	2	0	
	116	Entire 1914.....
	122	3	0	Nov. to end 1914.....
	133	115	1909	To death, Nov., 1914..	4	0	..	6	0	Nov. to end 1914.....
	141	5	0	
	147	5	0	
	118	3	0	Entire 1914.....
	153	3	0	Entire 1914.....
	154	4	0	To June, 1914.....
	159	4	0	

[illegible]

TABLE 22.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1914—(Continued)

1914	Zone 1			Zone 2			Zone 3					
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
435	232	1911	Entire 1914.....	3	0
439	Entire 1914.....	6	0
443	236	Mar. to Fall, 1914....	14	0	To Mar., 1914.....	14	0
Greene 102	987	1908	Mar. to July, 1914..... (No data to Mar.; moved July)	7	0	July to end 1914..... (New family)	8	0
103	987	Mar. to July, 1914....	5	0	To Mar., 1914.....	5	0
110	987	May to July, 1914.... (No data to May; moved July)	7	0	July to end 1914..... (New family)	4	0
111	987	Mar. to July, 1914....	9	0	July to end 1914.....	9	0
118	Entire 1914.....	11	0
136	See 272 Brawley	Entire 1914.....	7	0
146	1256	1914	Dec. to end 1914..... (New family; family of Case 1286 not counted here)	1	0	To Dec., 1914..... (Moved Dec.)	10	0
154	1286	Dec. to end 1914.....	4	0	To Dec., 1914.....	4	0
162	940	1914	Oct. to end 1914.....	940	Oct. to end 1914.....	8	0	To Oct., 1914.....	8	0
172	(New family; count- ed at 159 Laurens for 1914)	989, 197	To June, 1914.....	7	0	June to Oct., 1914.... (Moved Oct.)	7	0
181	No data for 1914	1293, 16, 222	Summer to end 1914... (No data to Summer)	2	0			
196	See 305 Forest	16, 1293, 1267, 796, 197, 989, 222	Entire 1914.....	8	0			
201	See 304 Forest	1267, 796, 198, 222, 1293	Entire 1914.....	6	0			
206					
216					
217	222	1911	May to Aug., 1914..... (No data to May; moved Aug.)	5	0					
226	1293	1913	Aug. to end 1914..... (New family; count- ed at 327 Forest)	0	0					
	198, 222, 1293, 893	Entire 1914.....	5	0			

Howard	187	500	1913	To June, 1911.....	500	To June, 1911.....	1	0	June to end 1911.....	5	0
188	501	1912	Apr. to May, 1914.....	501	Sept. to end 1911.....	7	0	June to Sept., 1911.....	7	0	
189	502	1912	(No data to Apr.; away May to Sept., 1914)	502	May to June, 1911.....	1	0				
204	1419	1912	Sept. to end 1911 (Returned Sept.)	1419							
205	1420	1912		1420							
212	1421	1912		1421							
218	1422	1912		1422							
222	1423	1912		1423							
230	1424	1912		1424							
236	1425	1912		1425							
254	1426	1912		1426							
264	1427	1912		1427							
316	1428	1912		1428							
Jennings	110	1912		110							
111	1912	1912		111							
118	1290	1912		1290							
119	1291	1912		1291							
126	1292	1912		1292							
127	1293	1912		1293							
134	1294	1912		1294							
135	1295	1912		1295							
142	1296	1912		1296							
143	1297	1912		1297							
150	1298	1912		1298							
151	1299	1912		1299							
158	1300	1912		1300							
155	1301	1912		1301							
166	1302	1912		1302							
167	1303	1912		1303							
	1304	1912		1304							
	1305	1912		1305							
	1306	1912		1306							
	1307	1912		1307							
	1308	1912		1308							
	1309	1912		1309							
	1310	1912		1310							
	1311	1912		1311							
	1312	1912		1312							
	1313	1912		1313							
	1314	1912		1314							
	1315	1912		1315							
	1316	1912		1316							
	1317	1912		1317							
	1318	1912		1318							
	1319	1912		1319							
	1320	1912		1320							
	1321	1912		1321							
	1322	1912		1322							
	1323	1912		1323							
	1324	1912		1324							
	1325	1912		1325							
	1326	1912		1326							
	1327	1912		1327							
	1328	1912		1328							
	1329	1912		1329							
	1330	1912		1330							
	1331	1912		1331							
	1332	1912		1332							
	1333	1912		1333							
	1334	1912		1334							
	1335	1912		1335							
	1336	1912		1336							
	1337	1912		1337							
	1338	1912		1338							
	1339	1912		1339							
	1340	1912		1340							
	1341	1912		1341							
	1342	1912		1342							
	1343	1912		1343							
	1344	1912		1344							
	1345	1912		1345							
	1346	1912		1346							
	1347	1912		1347							
	1348	1912		1348							
	1349	1912		1349							
	1350	1912		1350							
	1351	1912		1351							
	1352	1912		1352							
	1353	1912		1353							
	1354	1912		1354							
	1355	1912		1355							
	1356	1912		1356							
	1357	1912		1357							
	1358	1912		1358							
	1359	1912		1359							
	1360	1912		1360							
	1361	1912		1361							
	1362	1912		1362							
	1363	1912		1363							
	1364	1912		1364							
	1365	1912		1365							
	1366	1912		1366							
	1367	1912		1367							
	1368	1912		1368							
	1369	1912		1369							
	1370	1912		1370							
	1371	1912		1371							
	1372	1912		1372							
	1373	1912		1373							
	1374	1912		1374							
	1375	1912		1375							
	1376	1912		1376							
	1377	1912		1377							
	1378	1912		1378							
	1379	1912		1379							
	1380	1912		1380							
	1381	1912		1381							
	1382	1912		1382							
	1383	1912		1383							
	1384	1912		1384							
	1385	1912		1385							
	1386	1912		1386							
	1387	1912		1387							
	1388	1912		1388							
	1389	1912		1389							
	1390	1912		1390							
	1391	1912		1391							
	1392	1912		1392							
	1393	1912		1393							
	1394	1912		1394							
	1395	1912		1395							
	1396	1912		1396							
	1397	1912		1397							
	1398	1912		1398							
	1399	1912		1399							
	1400	1912		1400							
	1401	1912		1401							
	1402	1912		1402							
	1403	1912		1403							
	1404	1912		1404							
	1405	1912		1405							
	1406	1912		1406							
	1407	1912		1407							
	1408	1912		1408							
	1409	1912		1409							
	1410	1912		1410							
	1411	1912		1411							
	1412	1912		1412							
	1413	1912		1413							
	1414	1912		1414							
	1415	1912		1415							
	1416	1912		1416							
	1417	1912		1417							
	1418	1912		1418							
	1419	1912		1419							
	1420	1912		1420							
	1421	1912		1421							
	1422	1912		1422							
	1423	1912		1423							
	1424	1912		1424							
	1425	1912		1425							
	1426	1912		1426							
	1427	1912		1427							
	1428	1912		1428							
	1429	1912		1429							
	1430	1912		1430							
	1431	1912		1431							
	1432	1912		1432							
	1433	1912		1433							
	1434	1912		1434							
	1435	1912		1435							
	1436	1912		1436							
	1437	1912		1437							
	1438	1912		1438							
	1439	1912		1439							
	1440	1912		1440							
	1441	1912		1441							
	1442	1912		1442							
	1443	1912		1443							
	1444	1912		1444							
	1445	1912		1445							
	1446	1912		1446							
	1447	1912		1447							
	1448	1912		1448							
	1449	1912		1449							
	1450	1912		1450							
	1451	1912		1451							
	1452	1912		1452							
	1453	1912		1453							
	1454	1912		1454							
	1455	1912		1455							
	1456	1912		1456							
	1457	1912		1457							
	1458	1912		1458							
	1459	1912		1459							
	1460	1912		1460							
	1461	1912									

TABLE 22.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1914—(Continued)

1914	Zone 1				Zone 2				Zone 3			
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
171	1167, 1312, 1026	Entire 1914.....	7	0	Mar. to end 1914.....	3	0
175	1167	To Mar., 1914.....	3	0			
181	1167	1913	To Mar., 1914..... (Moved Mar.; no further data)	5	0							
182	1312, 1026	June to end 1914..... (No data to June)	4	0			
Johnson	Entire 1914.....	4	0
	To Aug., 1914..... (Moved Aug.; no further data)	5	0
116	Entire 1914.....	2	0
117	Entire 1914.....	5	0
122	Entire 1914.....	3	0
223	To Aug., 1914.....	5	0
			To Aug., 1914; no further data for 1914)		
127	116, 552	Entire 1914.....	7	0
128	116, 552	Entire 1914.....	5	0			
131	116, 552	Entire 1914.....	4	0			
134	116, 552	Entire 1914.....	2	0			
137	116	1909	Entire 1913.....	2	0							
140	552	1913	116, 552	Entire 1914.....	5	0			
141	116, 552, 590	Entire 1914.....	6	0			
146	590	Entire 1914.....	Entire 1914.....	4	0
147	590, 434	Entire 1914.....	5	0			
178	434	To Apr., 1914.....	4	0	Apr. to end 1914.....	4	0
Langford	No data for 1914			
	No data for 1914			
	No data for 1914			
			
			
Laurens	To Mar., 1914..... (Moved Mar.; count- ed at 145 Allen for 1914)	940	May to Oct., 1914..... (New family)	2	0	Entire 1914.....	2	0
	328	1912	Entire 1914.....	1	0
			
			
			
159	940	1914	May to Oct., 1914..... (Moved Oct.; no further data)	6	0	868, 328, 1376	To May, 1914.....	7	1			
Manning	115, 1358	Entire 1914.....	3	0			
110							

111	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
118	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
119	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
127	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
134	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
135	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
142	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
143	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
150	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
Milan	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
108	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
109	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
116	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
117	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
123	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
121	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
129	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
134	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
135	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
140	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
141	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
147	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
148	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
152	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
153	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
158	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
159	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
165	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0
166	1338	1913	Entire 1914	738, 1338, 1171	Entire 1911	6	0	To June, 1911	0

TABLE 22.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1914—(Continued)

1914	Zone 1					Zone 2			Zone 3		
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
					Total	Incident Cases			Total	Incident Cases	
Montgomery	134	1004	1911	Apr. to Fall, 1914..... (Moved Fall)	26	0	To Apr., 1914.....
	138	1004	Apr. to Fall, 1914.....	5	0	Fall to end 1914
	142	904, 977, 1259	Entire 1914.....	7	0	To Apr., 1914.....
	380	70	To Jan. 21, 1914.....	9	2	Fall to end 1914
Oliver	113	749	1910	977, 1259	June to end 1914.....	4	0	Jan. 21 to end 1914.....
	114	626	1911	To June, 1914.....
	110	625	1911	4	0	Entire 1914.....	5	0
	120	977	1914	June to end 1914..... (New family)	977, 736, 1259, 750	Entire 1914.....	4	0
127	1914	1259	1914	977, 444, 1259, 726, 1060	Entire 1914.....	4	0
	1911	626	1911	748, 726, 747, 750	Entire 1914.....	3	0
	748, 726, 747, 1060	Entire 1914.....	8	0
	128	3	0	Apr. to end 1914.....	2	0
135	0	0	203, 204, 651, 652, 653, 654, 1005	Apr. to June, 1914..... (New family; mov- ed June)	7	0
	130	8	0	Oct. to end 1914..... (New family)
	141	748	1911	Entire 1914.....	510, 511, 512, 737, 651, 652, 653, 654, 1005	To Fall, 1914.....	5	0
	142	747	1913	Entire 1914.....	1313, 1389 237, 1313, 1389	Entire 1914.....	5	0	Entire 1914.....
Vaughn	1	1060	1913	To Apr., 1914..... (Moved Apr.; family of Case 1060 count- ed at 344 College) To Apr., 1914..... (Moved Apr.)	4	0	Entire 1914.....
	2	510	1913	7	0
	1911	511	1911
	1913	512	1913
3	737	...	1913
	...	261	1911
	...	263	1911
	...	264	1911
Wolfe	111
	112
	114

115
	120
	121
	132

1975

1975

TABLE 23.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1915—(Continued)

1915	Zone 1				Zone 2				Zone 3				
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
					Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
	230	Entire 1915.....	3	0
	231	Entire 1915.....	9	0
	231	Entire 1915.....	3	0
	235	Entire 1915.....	6	0
	248	Entire 1915.....	5	0
	256	Entire 1915.....	5	0
	272	Entire 1915.....	5	0
	280	1286	To Apr., 1915.....	3	0	Apr. to end 1915.....	3	0
	283	Vacant house	1295	Mar. to end 1915.....	7	0	To Mar., 1915.....	12	0
	296	1295	Mar. to end 1915.....	11	0	To Mar., 1915.....	11	0
	302	Entire 1915.....	9	0
	303	Entire 1915.....	6	0
	306	Entire 1915.....	6	0
	309	Entire 1915.....	5	0
	312	To Aug., 1915..... (No further data)	9	0
	316	Entire 1915.....	7	0
	324	June to end 1915..... (No data to June)	9	0
	331	238, 1269	Entire 1915.....	4	0	Entire 1915.....	13	0
	339	68, 69, 238	Entire 1915.....	7	0	Entire 1915.....	9	0
	342	68, 69, 238,	Entire 1915.....	10	0	Entire 1915.....	9	0
	350	68, 1295	Entire 1915.....	16	0	Entire 1915.....	13	0
	360	68, 69, 238, 1295	Entire 1915.....	16	0	Entire 1915.....	6	0
	384	Entire 1915.....	6	0
	389	Vacant house	Entire 1915.....	3	0
	390	Entire 1915.....	5	0
	396	Entire 1915.....	5	0
	402	Entire 1915.....	8	0
Burnett	109	1290, 1288, 1291	Entire 1915.....	2	0	Entire 1915.....	4	0
	110	Entire 1915.....	4	0
	117	1336, 555, 1303, 1290, 1291	To Fall, 1915..... (Moved Fall; no further data for 1915)	3	0	Entire 1915.....	4	0
	118	1303, 555, 1309, 913, 939, 444	Entire 1915.....	5	0	Entire 1915.....	4	0
	127	555	1911	To Feb., 1915..... (Moved Feb.)	5	0	1290, 944, 1291, 64,	Feb. to June, 1915..... (New family)	9	1	Entire 1915.....	4	0
	128	1303	1915	June to end 1915.....	8	0	1336, 65, 1255	Entire 1915.....	7	0	Entire 1915.....	4	0
	128	1309, 939, 1303, 913, 444, 555, 64, 65	Entire 1915.....	7	0	Entire 1915.....	4	0
	131	Family counted at 149 Allen for 1915	Entire 1915.....	4	0

TABLE 23.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1915—(Continued)

House Street and Number	Zone 1					Zone 2			Zone 3	
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
260	1276, 987, 590	Entire 1915.....	8	0	
261	1276, 987, 738, 1425	Feb. to end 1915..... (No data to Feb.)	16	0	
265	987 1276	1908 1915	To Aug., 1915..... May 28 to Aug., 1915 (Moved Aug.; no further data)	7	1					
271	987, 1276, 1279, 738	Entire 1915.....	20	0	
272	738	1913	Entire 1915.....	6	0	738, 1279 738	Entire 1915.....	4	0	
277	Entire 1915.....	4	0	
282	Entire 1915.....
283	Entire 1915.....
291	8
291	6
297	1295	1914	See 288 Brawley See 296 Brawley Mar. to end 1915..... (Family of Case 1295 counted at 178 Far- ley for 1915)	6	0	1286, 590	To Mar., 1915.....	5	0	
298	590, 1297, 1295	Entire 1915.....	6	0	
303	590, 1297, 940, 1282, 1235	Entire 1915.....	4	0	
304	590	1913	To May 1, 1915..... (Moved May)	9	0	1297, 590	Mar. to end 1915..... (No data to Mar.)	10	0	
310	1297	1914	May to end 1915..... (New family)	5	0	1297, 590, 940, 1282	Entire 1915.....	5	0	
311	16, 197, 989, 940, 1282	To Nov., 1915.....	7	0	
317	796, 1267, 16, 1283, 1280	Apr. to end 1915.....	8	0	
325	197 989	1912 1913	To Apr., 1915..... (Moved Apr.)	12	0					Nov. to end 1915.....
331	1267 796	1914 1913	Entire 1915..... To May, 1915 (Moved May)	12	0					7
334	1280	1915	July to end 1915.....	10	0	796, 619, 1267, 989, 197, 977, 1259	To July, 1915.....	11	1	
337	1267, 328, 1289, 619, 1293	May to end 1915..... (No data to May)	6	0	
338	619	1913	Apr. to May, 1915..... (No data to Apr.; moved May)	7	0	796, 1280, 625	June to end 1915..... (New family)	7	0	

[illegible]

House Street and Number	Zone 1					Zone 2			Zone 3			
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
132	194	1910	203, 204	To June, 1915..... (Moved June) July to end 1915..... (New family)	2	0	Entire 1915.....	6	0
134 Duncan 103	1353	1913	Dec. to end 1915..... (Family of Case 1358 counted at 118 Manning for 1915)	5	0	To Dec., 1915.....	5	0
101	1353	Dec. to end 1915.....	4	0	To Dec., 1915.....	4	0
113	1353	Dec. to end 1915.....	4	0	To Dec., 1915.....	3	0
114	1358	Dec. to end 1915.....	3	0	To Dec., 1915.....	3	0
121	Entire 1915.....	7	0
122	Entire 1915.....	13	0
129	1348	Entire 1915.....	19	0	Entire 1915.....	2	0
130	1348	May to end 1915..... (No data to May)	7	0	Apr. to end 1915.....	18	0
137	515	To Apr., 1915.....	2	0	Apr. to end 1915.....	5	0
145	515	1910	To Apr., 1915..... (Moved Apr.)	13	0	1287	Apr. to end 1915.....	10	0	Apr. to end 1915.....	11	0
146	1283	1912	1287, 515	To Apr., 1915.....	18	0	To July 18, 1915.....	3	0
154 Farley 112	235	1911	515	Entire 1915.....	10	0	Sept. to end 1915..... (No data to Apr.)	6	0
116	436, 437, 438	Entire 1915.....	2	0	Sept. to end 1915.....	5	0
122	1436, 1427	3	0	Entire 1915.....	9	0
133	1426	1915	July 18 to Sept., 1915.....	8	0	July 18 to Sept., 1915.....	To May, 1915..... (Moved May)	7	0
141	1427	1915	Aug. 7 to Sept., 1915	1358, 1426, 1427	To Sept., 1915.....	5	0	Aug. to end 1915.....	9	0
147	1353	To Aug., 1915.....	9	0	To May, 1915.....	5	0
148	1174	June to end 1915..... (New family)	8	0	8	0
153	1174, 1269, 1358	Entire 1915.....	3	0	11	0
154	1174	1914	May to end 1915..... (New family)	7	0	To May, 1915..... (Moved May)	10	0
159	1269	Entire 1915.....	9	0	7	0
160	1174	May to Aug., 1915..... (No further data)	7	0	Entire 1915.....	8	0
166	238, 1295	To Mar., 1915.....	8	0	Mar. to end 1915.....	5	0
171	238, 1295	To Mar., 1915.....	4	0	Mar. to end 1915.....	11	0
172	238	1911	To Mar., 1915.....	12	0	To Mar., 1915.....	Mar. to end 1915..... (New family)	10	0
177	1295	1914	(Moved Mar.)	5	0	Mar. to end 1915.....
178	To Mar., 1915..... (Moved Mar.)

[illegible]

TABLE 23.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1915—(Continued)

1915	Zone 1					Zone 2			Zone 3		
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
					Total	Incident Cases			Total	Incident Cases	
110	508 1279	1913 1915	June to end 1915.....	.. 3	.. 0	987, 1276	Mar. to June, 1915.... (No data to Mar.)	8	1	To June, 1915.....
111	1279	June to end 1915.....	6	0	To June, 1915.....
118	1279	June to end 1915.....	11	0
119	1279	Aug. to end 1915.... (No data to Aug.)	6	0
136	See 272 Brawley	7	0	1295	Apr. to end 1915.....	5	0
146	1286	1914	To Apr., 1915..... (Moved Apr.)	1286, 1295	Entire 1915.....	5	0
151	910, 1282, 1295	Entire 1915.....	6	0
162	Sept. to end 1915.....
172	940 1282	1914 1915	To Sept., 1915..... June to Sept., 1915 (Moved Sept.)	10	1
181	Mar. to end 1915..... (No data to Mar.)
181	See 305 Forest	16	0	16, 328, 1285, 1289, 1293	To Sept., 1915..... Oct. to end 1915	16	0
196	See 304 Forest	12	0
201	880	1911	Sept. to Oct., 1915.....	3	0	3	1
206	1293	1913	Entire 1915.....	2	0	328, 1289, 1293	To May., 1915.....	5	0
216	328	1912	Feb. to end 1915.....	1285, 328, 910, 1289, 1293, 1282	Entire 1915.....	7	0
217	1289	1914	(No data to Feb.)
217	1285	1915	May to Sept., 1915..... (Moved Sept.)
226	940 1282	1914 1915	Sept. to end 1915 (New family; counted at 172 Greene for 1915)	9	0	12	0
Howard
187
193
199	484	1912	Entire 1915.....	7	0	434	Entire 1915.....	5	0
201	493	1913	434	Entire 1915.....	4	0
205
212	1419	1912
218
222
220	917, 918, 919, 920	Entire 1915.....	12	0
236	917 918	1914 1914	Entire 1915.....	9	0

TABLE 23.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1915—(Continued)

1915	Zone 1					Zone 2			Zone 3			
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
House Street and Number												
Johnson 111	590	Dec. to end 1915.....	10	0	Feb. to Dec., 1915..... (No data to Feb.)	10	0
112	500	1913	Dec. to end 1915..... (Family counted at 304 College)	Mar. to Dec., 1915..... (No data to Mar.)	7	0
116	590	Dec. to end 1915.....	2	0	To Dec., 1915.....	2	0
117	590	Dec. to end 1915.....	6	0	To Dec., 1915.....	6	0
122	445	To July 30, 1915.....	8	0	July 30 to end 1915.....	5	0
123	445	June to July, 1915..... (No data to June)	3	0	July 30 to end 1915.....	5	0
127	445	1907	To July 30, 1915..... (Moved July; no fur- ther data for 1915)	3	0
128	116, 552, 445	Entire 1915.....	5	0
131	116, 552, 445	Entire 1915.....	4	0
134	116, 552, 445, 590	Entire 1915.....	2	0
137	116 552	1909 1913	Entire 1915.....	2	0	5	0
140	500	1913	May to June, 1915..... (New families; fam- ily of Case 590 counted at 304 Col- lege; no further data for 1915)	3	0	116, 552	To Mar., 1915..... (Moved Mar.)
141	116, 552, 590	Feb. to end 1915..... (No data to Feb.)	3	0
146	590	May to June, 1915.....	4	0	To May, 1915..... June to end 1915	4	0
147	434	Entire 1915.....	5	0	Entire 1915.....	5	0
178
Langford 1	16	1908	Nov. to end 1915 (No data to Nov.; family counted at 304 Forest)
2	No data for 1915
3	No data for 1915
4	No data for 1915	445	Aug. to end 1915.....	1	0	Entire 1915.....	3	0
5	To Aug., 1915.....	1	0
Laurens 153	Mar. to end 1915..... (No data to Mar.)	1	0

159	413, 912, 863	Aug. to end 1915. (No data to Aug.)	5	0				
Manning	1426, 1427, 1338, 1425	To Fall, 1915.	6	0			Fall to end 1915.	6
110	1338, 1425	To Fall, 1915.	7	0			Fall to end 1915.	5
111	1338	1425	Aug. to Fall, 1915.	2	0			Fall to end 1915.	2
118	738	Fall to end 1915. (New family)	7	0				
119	1425	738, 1269, 1125	July 30 to end 1915. (No data to July 30, 1915)	7	0				
127	1338, 1269, 1425	Entire 1915.	10	0				
134	1269	Entire 1915.	6	0				
135	1269	1269	Entire 1915.	8	0				
142	1269	Entire 1915.	5	0				
143	1171						
150	1172						
	1173						
Milan						
103					Entire 1915.	9
109	590	Dec. to end 1915.	4	0			To Dec., 1915.	4
116					Entire 1915.	9
117	590	Dec. to end 1915.	8	0			To Dec., 1915.	8
123					Entire 1915.	5
124	483					To Feb., 1915.	3
					(Moved Feb.)	
					Feb. to end 1915.	33
					(New families)	
128	1005, 651, 652, 653	Entire 1915.	12	0				
129	1005, 651, 652, 653	Entire 1915.	6	0				
134	1005						
	651						
	652						
	653						
	654						
135	590, 651, 652, 653,	Entire 1915.	9	0				
	1005	...						
140	651, 652, 653, 1005	Entire 1915.	4	0				
141	590, 651, 652, 653,	Entire 1915.	6	0				
	1005	...						
147					Entire 1915.	4
148					Entire 1915.	5
152					Entire 1915.	5
153					Entire 1915.	3
158					Entire 1915.	4
159					Entire 1915.	4
165					Entire 1915.	10
	917, 918, 919, 920	Entire 1915.	11	0				
166					Entire 1915.	8

TABLE 23.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1915—(Continued)

1915	Zone 1				Zone 2			Zone 3	
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population Total Incident Cases	Ante- cedent Case	Time in Zone 2	Exposed Population Total Incident Cases	Time in Zone 3	Exposed Population Total Incident Cases
House Street and Number									
Montgomery 131 133 142 }	1427	1915	July 15 to Aug. 7, 1915. (Family of Case 1427 counted at 133 Far- ley)	22 0	To July 15, 1915..... Aug. 7 to end 1915	23 0
380	1427	July 15 to Aug. 7, 1915 (Moved Aug.)	5 0	To July 15, 1915..... Aug. 7 to end 1915..... (New family)	5 0 0
Oliver 113	749	1910	625, 977, 1250, 904	Entire 1915.....	8 0
114	625, 1250, 977, 1280	Entire 1915.....	6 0
119	625	1911	To Sept., 1915.....	4 0	625	Sept. to end 1915.....	4 0
120	977 1259	1914 1914	To Mar., 1915..... (Moved Mar.; family of Cases 977 and 1259 counted at 100 Burnett)	3 0	625, 1280, 619	Mar. to end 1915.....	5 0
127	625, 977, 1259	Entire 1915.....	7 0
128	625	1911	Sept. to end 1915.....	5 0	625, 796, 977, 1259, 619	To Sept., 1915.....	6 0
135	625, 748	Entire 1915.....	3 0
136	748, 796, 625	Entire 1915.....	7 0
141	748	1911	Entire 1915.....	3 0	748	Entire 1915.....	7 0
142	747	1913	Entire 1915..... Entire 1915.....	10 0 0
Vaughn 1 2	261 263 264 265	1911 1911 1911 1910	Entire 1915.....	9 0
3
Wolfe 110 (New house)	1389	1914	Sept. to end 1915 (No data to Sept.; family counted at 127 Colton)
111	1389	Sept. to end 1915.....	10 0	To Sept., 1915.....	10 0
112	1313, 1314, 1389	Entire 1915.....	5 0
114	237, 1313, 1314, 1389	Mar. to end 1915..... (No data to Mar.)	4 0
115	237	Entire 1915.....	8 0	Entire 1915.....	6 0
120	Entire 1915.....	7 0
121	Entire 1915.....	2 0
132

TABLE 24.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1916

House Street and Number	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population Total	Ante- cedent Case	Time in Zone 2	Exposed Population Total	Time in Zone 3	Exposed Population Total	Incident Cases
Allen										
115	415, 1235	Entire 1916 to date....	4	Entire 1916 to date....	6	0
117	415	Entire 1916 to date....	3	Entire 1916 to date....	2	0
118	415	Entire 1916 to date....	3	Entire 1916 to date....	13	0
124	Entire 1916 to date....	4	9	Entire 1916 to date....	5	0
127	445	1907	415, 1235	Entire 1916 to date....	9	Entire 1916 to date....	3	0
128	Entire 1916 to date....	3	0
130	Entire 1916 to date....	4	0
131	Entire 1916 to date....	6	0
137	Entire 1916 to date....	10	0
141	Entire 1916 to date....	8	0
145	Entire 1916 to date....	8	0
148	Entire 1916 to date....	12	0
149	Entire 1916 to date....	6	0
Arch	Entire 1916 to date....	10	0
371	Entire 1916 to date....	5	0
379	1371, 1382,	June, 1916, to date....	12	Entire 1916 to date....	8	0
385	1383	June, 1916, to date....	6	To June, 1916.....	12	0
393	1374, 1382,	June, 1916, to date....	6	To June, 1916.....	6	0
397	1383	Entire 1916 to date....	10	0
403	Entire 1916 to date....	7	0
409	Entire 1916 to date....	9	0
503	Mar., 1916, to date.... (No data to Mar.)	5	0
Brawley	Entire 1916 to date....	5	0
190	16, 1353	Entire 1916 to date....	9	Entire 1916 to date....	8	0
191	Entire 1916 to date....	5	0
194	No data for 1916	...	16, 1353	Entire 1916 to date....	7	Entire 1916 to date....	5	0
195	Entire 1916 to date....	5	0
196	16, 1353	Entire 1916 to date....	6	Entire 1916 to date....	10	0
197	Entire 1916 to date....	5	0
201	16, 1353	Entire 1916 to date....	6	Entire 1916 to date....	2	0
202	Entire 1916 to date....	3	0
204	Entire 1916 to date....	6	0
205	Entire 1916 to date....	3	0
218	Entire 1916 to date....	3	0
219	Entire 1916 to date....	9	0
224	Entire 1916 to date....	3	0
225	Entire 1916 to date....	3	0
230	Entire 1916 to date....	3	0
231	1371, 1372	Aug., 1916, to date.... (Not counted for 1916)	...	Entire 1916 to date....	6	0
234	To Aug., 1916.....	5	0
235	Entire 1916 to date....	4	0
248	Entire 1916 to date....	3	0
256	1419	Feb., 1916, to date....	3	To Feb., 1916.....	10	0
272	To June, 1916.....	13	0
280	Vacant house	To June, 1916.....	13	0
288	1396	June to July, 1916....	10	To June, 1916.....	10	0
296	1396, 1373	June, 1916, to date....	13	To June, 1916.....	13	0
302	1373	1915	June 27, 1916, to date....	5	1421	To June, 1916.....	3	To June, 1916.....	13	0

TABLE 24.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1916—(Continued)

House Street and Number	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
303	1121	1913	Entire 1916 to date....	5	0	1421, 1373	Entire 1916 to date....	5	0	
306	1373, 1421	Entire 1916 to date....	20	0	
312	1421	Entire 1916 to date....	9	0	
316	Entire 1916 to date....
324	Entire 1916 to date....
334	Entire 1916 to date....
339	Entire 1916 to date....
342	Entire 1916 to date....
350	68, 69	Entire 1916 to date....	7	0	
360	68, 69	Entire 1916 to date....	11	0	
381	68, 69	Entire 1916 to date....	10	0	
389	Vacant house	
390	Entire 1916 to date....
396	Entire 1916 to date....
402	Entire 1916 to date....
Burnett	Entire 1916 to date....
109	1290, 1291, 1288	Entire 1916 to date....	2	0	
110	No data to July 10, 1916; family not counted for 1916	
117	Entire 1916 to date....
118	444, 944, 1309	Entire 1916 to date....	5	0	
127	1290, 1336, 1291, 65, 944	Mar., 1916, to date.... (No data to Mar.)	2	0	
128	941	1914	Apr., 1916, to date....	6	0	65, 1300, 944	To Apr., 1916.....	5	0	
131	Family counted at 149 Allen for 1916	
135	64* 65	1910 1910	Entire 1916 to date (No other members of family)	
141	No data to July 12, 1916; family not counted for 1916	
145	1337	1913	To July, 1916..... (Moved July; no fur- ther data for 1916)	3	0	
152	198 1301	1911 1915	Entire 1916 to date....	3	0	
153	1255, 911, 198, 1301, 703, 736, 1418, 1259, 977, 626, 627, 1337	Entire 1916 to date....	10	0	

* Pellagrins designated in this manner are not considered active centers of the disease in this year.

[illegible]

TABLE 24.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1916—(Continued)

1916	Zone 1				Zone 2			Zone 3				
	Ante- cedent Case	First Dry- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
297	1396	1916	June to July, 1916.....	10	0	1396, 1373 June, 1916, to date....	7	0	To June, 1916.....	11	0
298	1396	June to July, 1916....	8	0	To June, 1916.....	7	0
303	1396	June to July, 1916....	6	0	To June, 1916.....	5	0
304	May to June, 1916....	6	0
310	(No data to May)	17	0
311	Entire 1916 to date....	6	0
317	Entire 1916 to date....	2	0
325	1267	1914	1280, 1405	Entire 1916 to date....	8	0	To June, 1916.....		
331	1167	1913	1280, 1405	Entire 1916 to date....	8	0	(No further data)		
334	1280	1915	To May, 1916.....	6	0							
	1405	1913	(Moved May)	3	0							
	Feb., 1916, to date....							
337	(New family)							
	1280, 328, 1405, 1280, 1357	Entire 1916 to date....	4	0			
338	1280, 1405, 625	Entire 1916 to date....	7	0			
343	328, 1280, 1285	To Apr., 1916.....	3	0			
	796	1913	625, 1396, 1285	(Moved Apr.; no further data)	5	0			
	Entire 1916 to date....	3	0			
347	893 1285	1912 1915	625	(Family of Case 796 moved Apr.; not counted here)	2	0			
	To Mar., 1916.....	3	0			
348	796 1396	1913 1916	1285	Mar. to July, 1916....	2	0			
	(No data to Mar.)	11	0			
Colton 100	Family counted at 110 Colton	944, 444, 1313, 1314, 1309	Entire 1916 to date....	11	0			
110						
116	444 939 913	1907 1914 1914	6	0							
	1309	1914	Entire 1916 to date.....							
119	1313 1314	1912 1915	Entire 1916 to date (No other members of family)							

[illegible]

TABLE 24.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1916—(Continued)

1916	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population Total	Ante- cedent Case	Time in Zone 2	Exposed Population Total	Time in Zone 3	Exposed Population Total	Incident Cases
Farley	437, 438	Entire 1916 to date...	3	Entire 1916 to date...	4	0
112	Entire 1916 to date...	3	0
116	Entire 1916 to date...	4	0
122	Feb. to July, 1916.... (Moved July; no further data)	5	0
133	Entire 1916 to date...	9	0
141	To June, 1916.... (Moved June; no further data)	8	0
147	Entire 1916 to date...		
148	1374	1911	Aug., 1916, to date (No data to Aug.; family counted at 138 Duncan for 1916)			
153	1174	1914	Entire 1916 to date...	8	0
154	Entire 1916 to date...	3	0
159	Mar., 1916, to date.... (No data to Mar.)	7	0
160	Entire 1916 to date...	7	0
165	Entire 1916 to date...	8	0
171	Entire 1916 to date...	3	0
172	Entire 1916 to date...	15	0
177	Entire 1916 to date...	10	0
178	Entire 1916 to date...	3	0
189	See 360 Brawley	Entire 1916 to date...	6	0
190	Entire 1916 to date...	7	0
208	1358	Entire 1916 to date...	10	Entire 1916 to date...	3	0
213	1358	Entire 1916 to date...	7	Entire 1916 to date...	6	0
214	Entire 1916 to date...	6	0
221	Entire 1916 to date...	6	0
222	Entire 1916 to date...	6	0
229	Entire 1916 to date...	6	0
230	1348	Entire 1916 to date...	5	Entire 1916 to date...	6	0
237	1348	Entire 1916 to date...	3	Entire 1916 to date...	6	0
238	1348	1914	Entire 1916 to date...	5	1348	Entire 1916 to date...	5	Entire 1916 to date...	6	0
245	748	Entire 1916 to date...	5	Entire 1916 to date...	6	0
246	1348	Entire 1916 to date...	10	Entire 1916 to date...	6	0
253	748	Feb., 1916, to date.... (No data to Feb.)	5	Entire 1916 to date...	6	0
251	1287	1913	Entire 1916 to date...	10	0
Forest	Entire 1916 to date...	3	0
272	Entire 1916 to date...	3	0
276	1399, 1400	June, 1916, to date...	14	Entire 1916 to date...	3	0
301	1280, 1405	Entire 1916 to date...	16	To June, 1916....	14	0
305			

[illegible]

TABLE 24.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1916—(Continued)

1916	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
217	940	1914	Entire 1916 to date.... June to July 15, 1916	5	1	940, 1282, 1351, 1285	Mar., 1916, to date.... (No data to Mar.)	8	0	
226	Entire 1916 to date.... Spring to July, 1916...
Howard	434, 590	To Spring, 1916,..... July, 1916, to date	7	0	8
187	Spring to July, 1916....
193	434	1912	To Spring, 1916,..... (Moved Spring)	7	0	
199	590	1913	July, 1916, to date (Family of Case 590 counted at 112 Johnson)	
204	493	1913	1419, 590	To Feb., 1916,..... July, 1916, to date	3	0	3
205	434, 590	To Spring, 1916,..... July, 1916, to date	5	0	5
212	1419	1912	To Feb., 1916 (Moved Feb.; no further data; fam- ily counted at 118 Greene)	
218	1419	To Feb., 1916,.....	6	0	6
222	Entire 1916 to date....	12	0	2
230	917	1914	Entire 1916 to date....	7	0	917	
236	918	1914	
254	919	1914	Entire 1916 to date....	4	0	Entire 1916 to date...	5	0	
264	920	1914	437, 438	
316	937	1910	Entire 1916 to date....	6	0	
Jennings	938	1913	1283, 1290, 1291	Entire 1916 to date....	
110	1283	1910	Entire 1916 to date....	2	0	6	0	
111	Entire 1916 to date....	
118	1290	1912	1	0	
119	1291	1912	1290, 1291, 1336	May, 1916, to date.... (No data to May)	4	0	
126	1292	1912	Entire 1916 to date....	3	0	1290, 1291, 1336	Entire 1916 to date...	4	0	
127	65, 1337, 1336, 1255, 944	Entire 1916 to date....	4	0	
134	

[illegible]

TABLE 24.—DOMICILE RELATIONSHIP—SPARTAN MILLS—1916—(Continued)

1916	Zone 1					Zone 2			Zone 3			
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
Langford 1 2 3 4 5	16 1353 1285	1908 1916 1915	Entire 1916 to date.... Apr. to Aug., 1916 July, 1916, to date.... (Family of Case 1285 counted at 347 Col- lege for 1916)	6 1	1 0	1353, 16 445, 1285 445	Mar., 1916, to date.... (No data to Mar.) ... Apr., 1916, to date.... (No data to Apr.) To July, 1916.....	2 .. 4 1	0 .. 0 0	Entire 1916 to date.... Entire 1916 to date....	2 0	0 0
	Laurens 163 159 Manning	... 1395 1269 ... 1171 1172 1173	... 1915 1914 ... 1911 1911 1911	Entire 1916 to date.... No data for 1916 ...								

135	651, 652, 653	Entire 1916 to date...	13	0	Entire 1916 to date...	4	0
140	651, 652, 653	Entire 1916 to date...	4	0	Entire 1916 to date...	5	0
141	651, 652, 653	Entire 1916 to date...	4	0	Entire 1916 to date...	5	0
147	Entire 1916 to date...	3	0
148	Entire 1916 to date...	4	0
152	Entire 1916 to date...	2	0
153	Entire 1916 to date...	8	0
158	Entire 1916 to date...	17	0
159	917	Entire 1916 to date...	5	0	Entire 1916 to date...	4	0
165	Entire 1916 to date...	8	0
166	Entire 1916 to date...	17	0
Montgomery	Entire 1916 to date...	4	0
134	Entire 1916 to date...	4	0
138	Entire 1916 to date...	8	0
142	Entire 1916 to date...	8	0
380	Entire 1916 to date...	8	0
Oliver	Entire 1916 to date...	8	0
113	749	1910	1280, 1405 625	Entire 1916 to date...	7	0	Entire 1916 to date...	3	0
111	1280, 1405, 625	Entire 1916 to date...	11	0	Entire 1916 to date...	3	0
119	Entire 1916 to date...	5	0	Entire 1916 to date...	3	0
120	Entire 1916 to date...	7	0	Entire 1916 to date...	3	0
127	Entire 1916 to date...	4	0	Entire 1916 to date...	3	0
128	625	1911	625, 748	Entire 1916 to date...	8	0	Entire 1916 to date...	3	0
135	625, 748, 1398	Entire 1916 to date...	5	0	Entire 1916 to date...	3	0
136	Entire 1916 to date...	5	0	Entire 1916 to date...	3	0
141	748	1911	Entire 1916 to date...	5	0	Entire 1916 to date...	3	0
142	747	1913	Entire 1916 to date...	5	0	Entire 1916 to date...	3	0
Vaughn	Entire 1916 to date...	5	0	Entire 1916 to date...	3	0
1	Entire 1916 to date...	5	0	Entire 1916 to date...	3	0
2	261	1911	1423	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
3	263	1911	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
3	264	1911	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
3	265	1910	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
3	1423	1915	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
Wolfe	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
109	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
(New house)	1389	1914	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
110	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
111	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
112	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
114	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
115	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
120	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
121	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0
132	Entire 1916 to date...	3	0	Entire 1916 to date...	3	0

The Archives of Internal Medicine

Vol. XX

SEPTEMBER, 1917

No. 3

THE ETIOLOGIC AGENT OF RAT BITE DISEASE

PRELIMINARY REPORT *

J. KITAGAWA, M.D., AND T. MUKOYAMA, M.D.

That there exists a particular form of disease due to rat bite has been long recognized in Japan, where incidents of rat bite have been more frequent than in certain other countries. Although some cases have been reported by American, as well as French, German, British and Spanish physicians, yet the establishment of a definite disease as a result of rat bite has been chiefly the work of Japanese observers. Miyake¹ and Crohn² have given exhaustive reviews of the subject, together with their own case reports.

As to the etiologic agent, Ogata³ thought it to be an organism belonging to the *Sporozoa*, while in German cases, the association of a streptothrix was reported by Schottmüller.⁴ In a recent article, Blake⁵ reports having obtained a pure culture of *Streptothrix muris ratti* of Schottmüller from a case of rat bite, by means of which he was able to reproduce in some rats local inflammation and proliferative lesions at the site of inoculation. The organism was nonpathogenic for guinea-pigs. Tileston⁶ adds two cases of rat bite, in the blood smears from one of which he found a streptothrix, while the second case failed to show any such organism. Recovery followed the injection of salvarsan in these cases. It may be recalled that as early as 1912, Hata⁷ recorded a series of cases of rat bite fever, where the intravenous administration of salvarsan at the febrile stage of the disease led to a complete and permanent cure in all but two instances, in which a second injection was required during the relapses. Of special significance is the recent

* Submitted for publication Jan. 26, 1917.

* From the Pathological Institute of the Medical School of Nagoya, Japan.

* This work was done under the direction of Prof. Dr. Hayashi.

* An abstract of this paper was published in Japanese Feb. 12, 1916, in Chuo-Igakkai.

1. Miyake, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1900, **5**, 231.

2. Crohn, B. B.: THE ARCHIVES INT. MED., 1915, **15**, 1014.

3. Ogata: Deutsch. med. Wchnschr., 1908, **34**, 1099.

4. Schottmüller, H.: Dermat. Wchnschr., 1914, **58**, Supplement, 77.

5. Blake, F. G.: Jour. Exper. Med., 1916, **23**, 39.

6. Tileston, W.: Jour. Am. Med. Assn., 1916, **66**, 995.

7. Hata, S.: München. med. Wchnschr., 1912, **59**, 854.

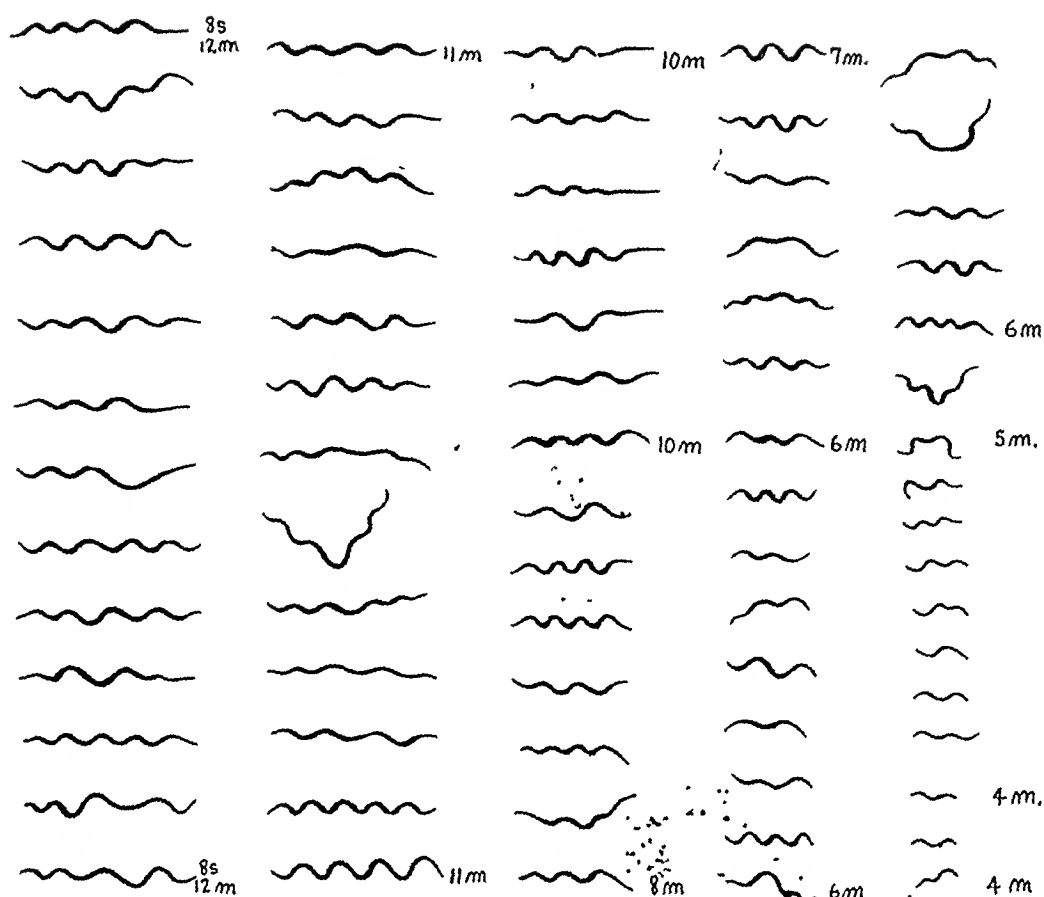


Fig. 5.—Principal forms of spirochetes of Type A found in the organs of the inoculated guinea-pig; s, spiral; m, micron.

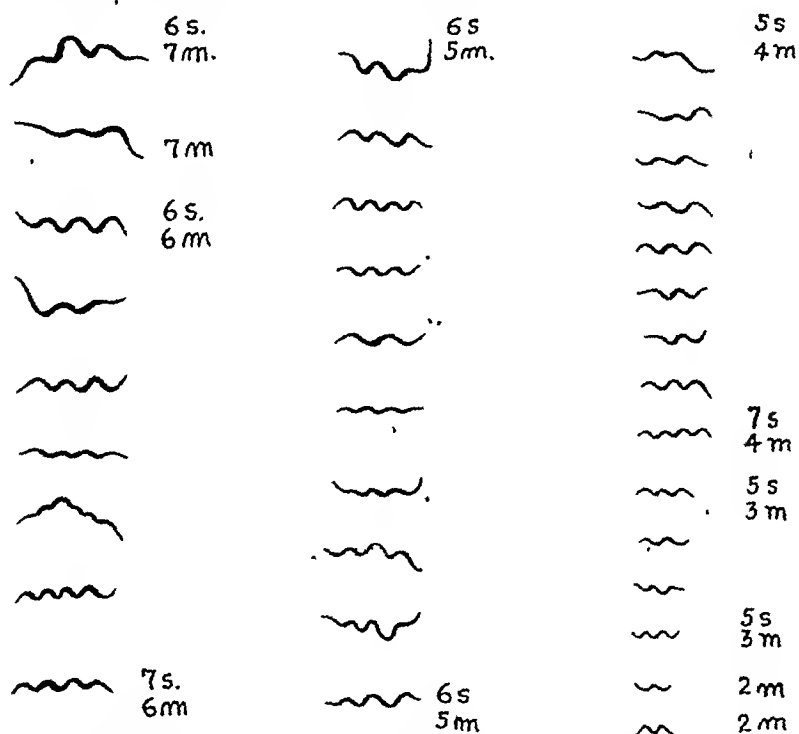


Fig. 6.—Principal forms of spirochetes of Type B found in the organs of the inoculated white rat; s, spiral; m, micron.

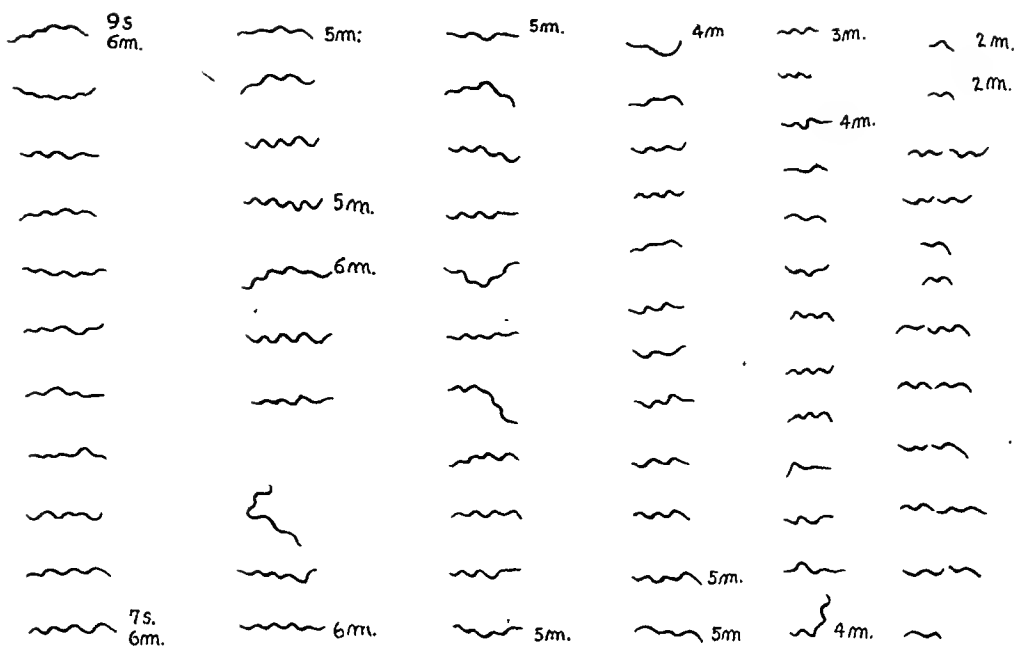


Fig. 7.—Spirochetes of Type B, obtained by inoculation of the splenectomized white rat (after previous subjection to Roentgen-ray treatment) with portions of the organs of another white rat containing spirochetes of Type B; *s*, spiral; *m*, micron.

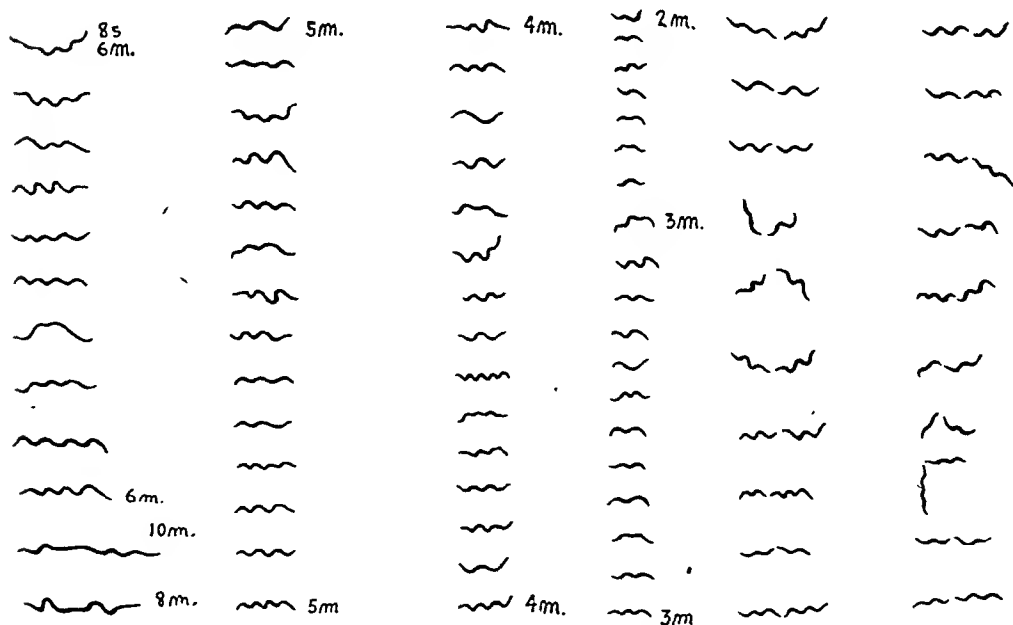


Fig. 8.—Varieties of form of spirochetes of Type B, obtained by inoculation of the splenectomized guinea-pig with the same organs as in Figure 4, 2, after previous subjection to Roentgen-ray treatment; *s*, spiral; *m*, micron.

conclude that the agent belongs to the group of protozoa that undergo gradual but marked modification with regard to form and toxicity. Moreover, since there is a definite period of incubation, followed by an eruption and swelling of the lymph glands, and since arsenic, especially salvarsan, is very efficacious in the treatment of the disease, our opinion is confirmed that we are dealing with a protozoan of the spirochetal variety.

The literature on the Wassermann reaction states that the reaction is positive in the case of such spirochetal diseases as relapsing fever, malaria, frambesia tropica and oriental sore. Dr. Kusunoki's experiments with this reaction, however, in five cases of rat bite fever showed it to be negative in four cases and positive in but one. It is possible, of course, that the latter subject had contracted a syphilitic infection at some time in the past. According to personal information received from Dr. Inada, the Wassermann reaction was negative in each of three cases of Weil's disease. It seems, therefore, that in rat bite disease and in some other spirochetal diseases we cannot place any reliance on the Wassermann reaction.

Repeated testing of the Wassermann reaction in one patient produced negative results. We therefore made an alcohol extract of the liver and heart of guinea-pigs harboring spirochetes of Type A, with which we made complement fixation tests. The complement fixation test was carried out twice in the case of a patient afflicted with rat bite fever with positive results. We applied the Wassermann reaction which also was positive. Subsequently, in order to prove whether or not our spirochetal antigen possessed any special peculiarity, we undertook experiments in complement fixation on patients suffering from rectal cancer, syphilis, and other similar diseases, at the same time applying the Wassermann test. The results of these experiments are given in the accompanying table.

RESULTS OF EXPERIMENTS IN COMPLEMENT FIXATION

Patient	Disease	Wassermann Reaction	Control	Reaction Spiro. Antigen	Control
Monkey.....	R. b. disease	±	±		
K.....	R. b. disease	—	—		
K.....	R. b. disease	+	—	+	—
K.....	R. b. disease	+	—	+	—
S.....	Rectal cancer	—	—	—	—
G.....	Syphilis	+	—	—	—
K.....	Syphilis	—	—	—	—
S.....	Syphilis	—	—	—	—
K.....	Syphilis	++	—	—	—
S.....	Syphilis	+	—	—	—
Y.....	Parenchymatous keratitis	—	—	—	—

It will be noticed that the reaction to the antigen of the spirochete of Type A proved positive in one case of rat bite disease.

Our organism of Type A not only possesses more spirals than does the spirochete discovered by Dr. Futaki in preparations stained with India ink but its curves are also much more regular. In comparison with those discovered by Dr. Futaki, the majority of our spirochetes, which are found in great quantities in our preparations, appear to belong to a different species. Yet they are nearly of the same size; moreover, irregularly shaped spirochetes, having fewer curves, were occasionally found in our preparations, so we at first concluded that Type A was of the same species as Dr. Futaki's spirochete. But another preparation of the variety discovered by Dr. Futaki, stained by the silver impregnation method of Levaditi, which had been found in the lymph gland of a patient, was exhibited at a meeting of the Pathological Society of Tokio, and from this specimen we were able to determine that these spirochetes were different from Type A. The organisms of Type B, however, seem to be identical with Dr. Futaki's specimen and also with those discovered at the same time by Dr. Ishiwara.

SUMMARY

The two types of spirochetes, found in the guinea-pigs and rat, respectively, not only varied considerably with respect to size, but also showed differences with regard to the distinctness of the spirals and the pointedness of the ends, which facts seem to us to indicate that these spirochetes belong to two different species. Yet, since the staining brought out no definite distinctions between them, and as they showed practically the same number of curves, it appears possible that the above-mentioned difference of form was a result of the differences existing between the inoculated animals, or that the spirochetes may have been in different stages of development. At all events, it is interesting to note that the spirochetes obtained from inoculation with the lymph gland and the lymph plasma derived from the same patient also appear to be of different sizes. Whether Type A and Type B are really identical, or, if they are not, which one is the etiologic agent, are points which cannot be determined without further investigation.

THE SALICYLATES

VIII. SALICYL EDEMA *

P. J. HANZLIK, M.D., R. W. SCOTT, M.D.

AND

J. L. REYCRAFT, M.D.

CLEVELAND

Following the administration of full therapeutic doses of salicylate there is a rather marked diminution in urine output, reaching its greatest depression about ten to twenty hours after the symptoms of toxicity appear and persisting for about forty to seventy hours after the administration of the drug. The output of urine reaches its previous level roughly about the time excretion of salicyl is completed.

Two possible explanations are suggested for this: (1) sweating; (2) retention of water, that is, edema; the important factors to be considered in retention are (a) tissues, and (b) kidney.

It is the object of this communication to report certain facts bearing on these causes. The work was conducted in a quantitative way and on persons some of whom were practically normal, others convalescent from various disorders. The following procedures were carried out before and after the administration of the salicylate, and throughout the experiment, which usually lasted about a week. The persons were weighed regularly, about three times in ten hours, and the drug was not administered until the weight curve became practically constant. This was reached usually within two to three days after the person was put to bed and placed on the regular routine. The water and dietary intakes were maintained as constant as possible throughout the procedure. Two hundred c.c. of water were administered every two hours. Coffee or milk was substituted for this at meal times. The meals were taken at the same hours, and the quantity was constant throughout. The administration of salicyl was so timed that the symptoms of toxicity would come when the stomach would be empty so as to avoid loss of contents in case emesis should occur. No attention was paid to the qualitative nature of the dietary, but even in this there were no radical changes, since the food in this hospital is remarkably constant in quality at all times.

* Submitted for publication April 14, 1917.

* From the Pharmacological Laboratory, Western Reserve University and the Medical Clinic, City Hospital, Cleveland.

* This investigation was supported, in part, by a grant from the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association.

Renal function was studied by the output of urine, which was collected in ten-hour periods; the quantitative excretion of albumin (method of Folin and Denis¹); and daily observations on the phenol-sulphonaphthalein excretion (two-hour, and carried out in the usual way) and urea nitrogen of the blood (by the urease, aeration and colorimetric procedure). Hemoglobin estimations were made with the idea of ascertaining the chief depot of the water retention, that is, whether the blood or tissues. For this, the carbon monoxid colorimetric method of Haldane² was chosen, using the Duboscq colorimeter for making the readings instead of test tubes. The results are expressed as relative percentages of hemoglobin. The effect on and the rôle of the tissues were also judged, in part by the course of salicyl excretion in the urine. The salicyl was estimated according to a method previously described.³ Sweating was judged, in part, from the weight curve and, in part, by direct inspection and the subjective symptoms reported by the patient himself.

When the weight and urine curves became practically constant, the salicylate was administered. A definite quantity (20 c.c.) of sodium salicylate (usually about 10 per cent.) was administered together with 80 c.c. of water every hour until toxicity, when the administration was stopped. The water intake was then maintained at the rate of 200 c.c. every two hours, and the various observations according to the procedures detailed above were carried out until the end of the experiment. In all, nine persons have been studied. Four of these (Patients 27, 28, 29 and 30) received sodium bicarbonate together with the salicylate. The detailed protocols for each individual are so long that they have been omitted entirely, and instead the data are presented in the form of curves for each one. Various clinical data pertaining to all the individuals are presented in the accompanying table.

1. *Salicylate Causes Edema.*—This is indicated by the fact that there is an increase in body weight demonstrable after the administration of the drug, unless this is prevented by sweating. Charts 1, 2, 3, 4, 6, 7 and 9 indicate definite increases in body weight and above the level before the drug was administered. This increase ranges from moderate to considerable. The diaphoresis ranged from imperceptible to just perceptible, and roughly, inversely proportional to changes in the body weight. That is, a relatively small diaphoresis is accompanied by a more marked increase in body weight.

Charts 5 and 8 show practically no changes in body weight. These persons gave evidences of marked diaphoresis. So far as other phe-

1. Folin and Denis: Jour. Biol. Chem., 1914, **18**, 273.

2. Haldane: Jour. Physiol., 1901, **26**, 497.

3. Thoburn and Hanzlik: Jour. Biol. Chem., 1915, **23**, 163.

TABLE OF CLINICAL DATA

Number and Patient	Diagnosis	Fluid and Dietary Intake	Total Quantity of Salicyl* Administered (gm.)	Diaphoresis	Remarks
21b (J. V.)	Normal; recovered from rheumatic fever	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	9.5	Imprecip- tible	
23 (J. E.)	Synechia cordis; chronic myocarditis	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	9.5	Marked	
24 (J. H.)	Chronic endocarditis and myocarditis	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 320 gm. food 3 times daily	8.1	Mild	
25 (H. V.)	Catarrhal conjunctivitis	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 320 gm. food 3 times daily	9.0	Mild	
26 (E. H.)	Corneal ulcer (left eye)	100 c.c. every hour for 7 hours 200 c.c. every 2 hours thereafter 320 gm. food 3 times daily	12.6	Marked	
27 (J. M.)	Varicose ulcer of leg.....	100 c.c. every hour for 7 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	12.6	Mild	14 gm. NaHCO ₃ administered together with salicyl
28 (T. S.)	Alcoholic gastritis	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	8.01	Moderate	9 gm. NaHCO ₃ administered together with salicyl
29 (L. K.)	Rheumatic fever (mild attack)	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	8.9	Marked	8 gm. NaHCO ₃ administered together with salicyl
30 (H. M.)	Chronic arthritis	100 c.c. every hour for 8 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	14.24	Just per- ceptible	16 gm. NaHCO ₃ administered together with salicyl

* Expressed as salicylic acid.

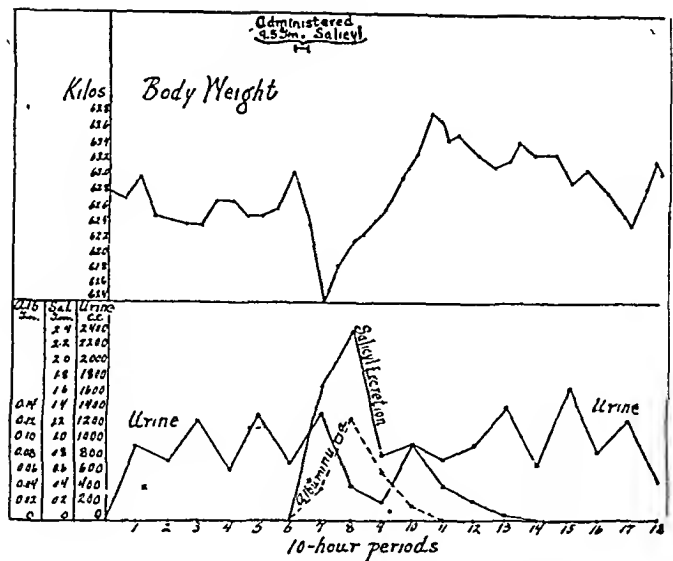


CHART 1.—Patient 21b (J. V.) In this and all the other charts the brace at the top of the chart indicates the period during which salicyl was administered; salicyl refers to salicylic acid; Alb, to albumin; sal, to salicyl; the cross X, to the quantity (grams) of feces voided; 'phthalein refers to phenolsulphonephthalein.

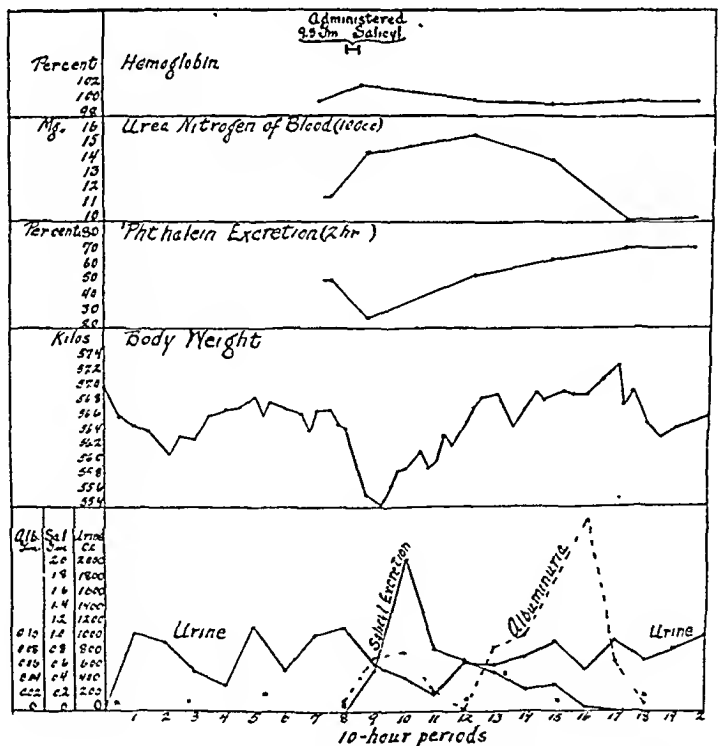


CHART 2.—Patient 23 (J. E.). Marked diaphoresis occurred from end of ninth to twelfth periods inclusive.

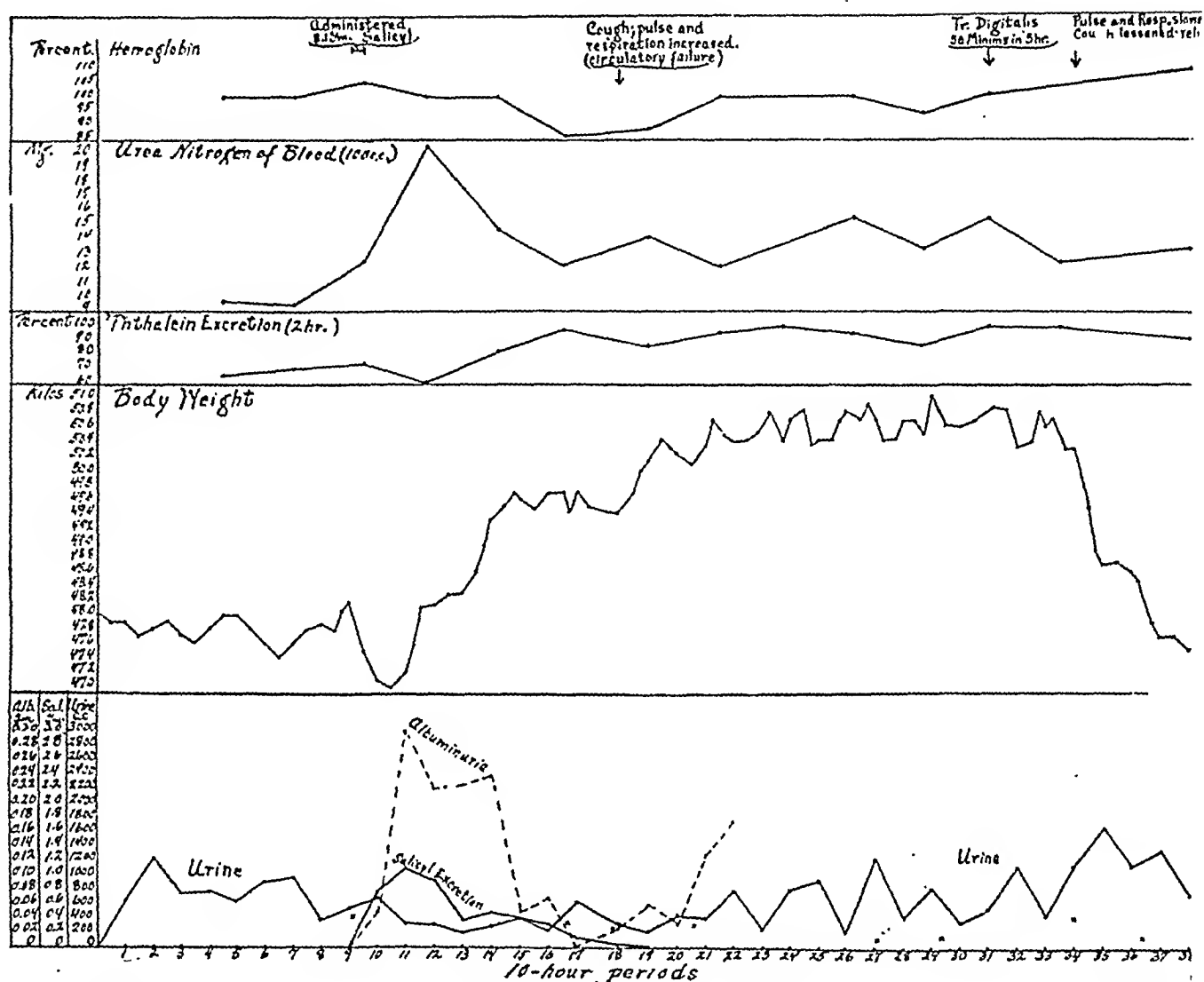


CHART 3.—Patient 24 (J. H.). Aside from the effects produced by the salicylate, this particular case presents an interesting study of digitalis action in circulatory embarrassment. About the time of appearance of certain objective symptoms, namely, increase in pulse rate, respiration and coughing, etc., there was demonstrable a dilution of the blood as indicated by a fall in the percentage of hemoglobin, diminution in the urea content of the blood, an increase in body weight and a diminution in water output. Gradually the blood became more concentrated because the tissues now became the chief reservoir for the surplus fluid. This is indicated also by the persistence of the edema. Renal function became variable as indicated by the variable excretion of phenolphthalein and urea content of the blood, the albuminuria at the same time being markedly increased. In the meantime the only subjective symptom was a slight sensation of oppression in the chest. On inspection there was some slight fulness of the face, but otherwise edema was not demonstrable. These effects had now lasted for about 160 hours. The question arose as to whether the marked increase in body weight was due to improved nutrition, in part or whole, or anasarca resulting from circulatory embarrassment. This was tested out by the administration of tincture of digitalis, the result being a prompt and marked fall in body weight to the original level with a marked increase in urine output, improvement of renal function and some concentration of the blood. The various effects are strikingly shown in the curves of the chart. It was concluded, therefore, that the increase in body weight was due to anasarca as the result of circulatory embarrassment.

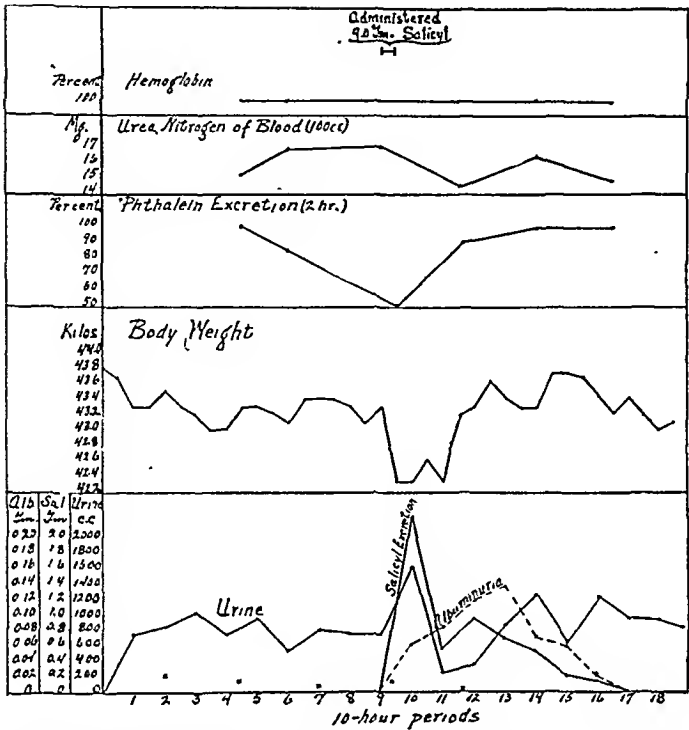


CHART 4.—Patient 25 (H. V.). Mild diaphoresis occurred from end of eleventh to thirteenth periods inclusive.

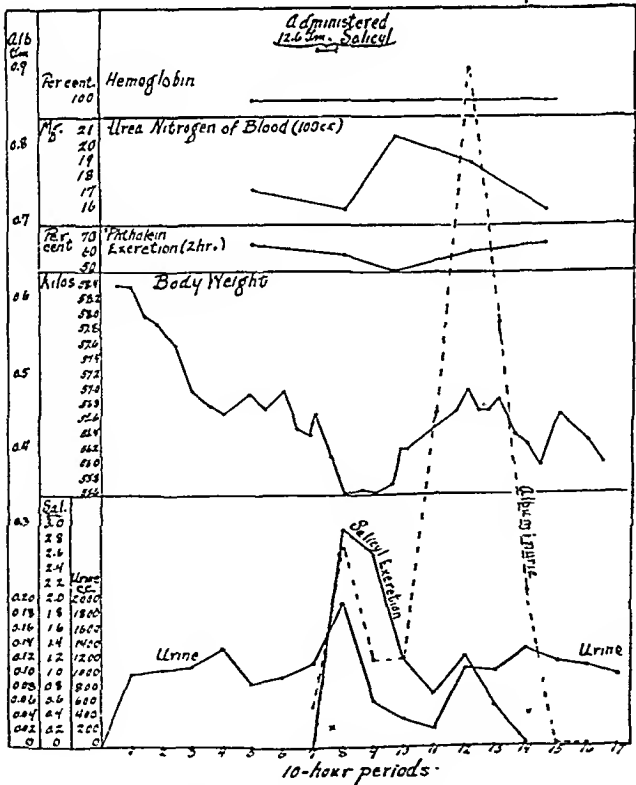


CHART 5.—Patient 26 (R. H.). Marked diaphoresis occurred from the ninth to end of eleventh periods inclusive.

nomena are concerned, these remained unchanged. In nearly every case there is evidence of a sharp decline in body weight about the time of toxicity. This is due, no doubt, to diaphoresis which occurs at this time and when the concentration of the drug in the tissues is at its maximum. This, of course, is a well known action of salicylate. Persistent sweating in those persons who habitually sweat considerably resulted in no modification of the curves of body weight. The loss of body weight cannot be attributed to increased urine or fecal output,

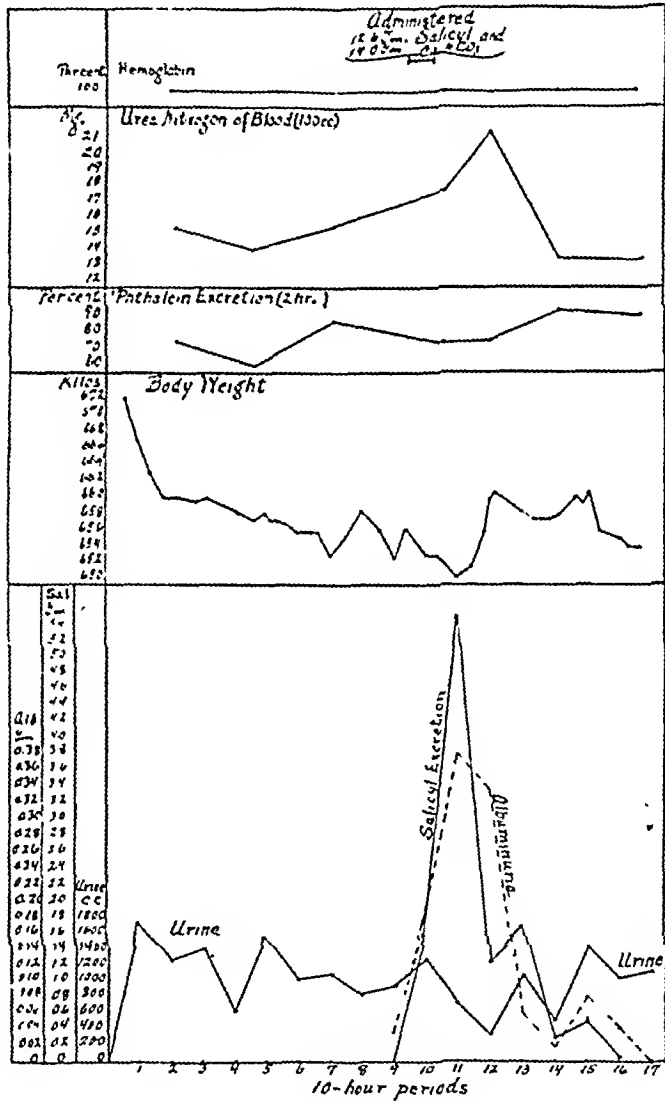


CHART 6.—Patient 27 (J. M.)

for these do not adequately compensate for the losses. The respiratory rate remained unchanged. The loss of water, therefore, could only have taken place by evaporation, that is, by diaphoresis.

It may be concluded that the administration of salicylate in full therapeutic doses causes a relative anuria, and this is due to retention of the water, that is, edema, as indicated by an increase in body weight unless modified by sweating.

2. *The Water Retention is not Due to Retention of Salicyl in the Tissues.*—This is indicated by the curves of salicyl excretion⁴ in all the figures, which represent the data obtained for different individuals. It is seen that the maximum excretion of salicyl occurs at a time when the body weight begins to increase and when the water excretion is lowest. The excretion is at its minimum when the body weight is at its maximum; that is, when the water retention or edema is most marked, and in most individuals this was completed before the body weight reached its previous level. The excretion of salicyl does not

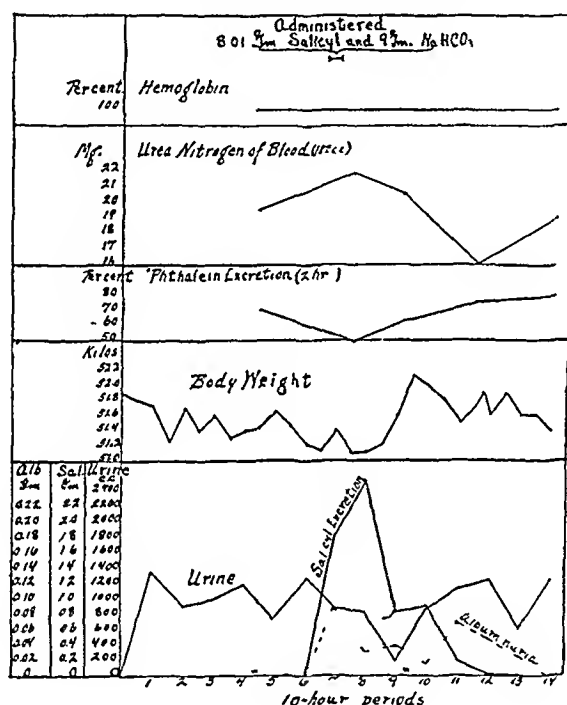


CHART 7.—Patient 28 (T. S.)

go parallel with the curve of body weight. There is no retention of salicyl and the retention of water, therefore, is not associated with or due to retention of salicyl in the tissues.

3. *The Water is not Retained by the Blood.*—This is indicated by the curves of hemoglobin percentage of the blood. Dilution of the blood was demonstrable in only one patient (24, Chart 3), in whom for a time there was some cardiac decompensation. On the other hand, an increase in the percentage of hemoglobin at toxicity was demonstrable in two patients. These persons sweated considerably from which it is inferred that there was some concentration of the blood at this time.

4. For other studies on the quantitative excretion of salicyl consult an earlier publication by Hanzlik, Scott and Thoburn: Jour. Pharmacol. and Exper. Therap., 1917, 9, 247, and in connection with retention, Jour. Pharmacol. and Exper. Therap., 1917, 9, 217.

In all other patients, whose blood was studied, no changes in blood volume were demonstrable.

From these evidences it appears logical to conclude that the water is retained in the tissues.

4. *The Retention is Chiefly of Renal Origin.*—Previous studies⁵ on renal function showed that the administration of salicylate impairs the functional efficiency of the kidney. This also is the case in the

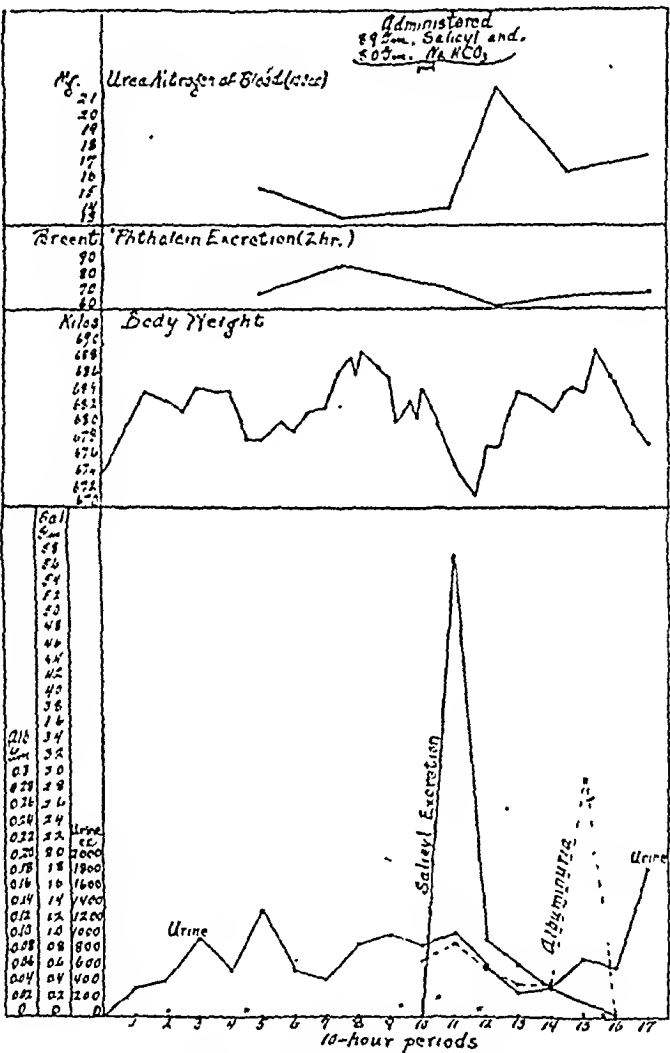


CHART 8.—Patient 29 (L. K.)

persons studied in connection with edema. Indeed it is one of the most constant features of the experiments, and is indicated in the various curves by a diminution in phenolsulphonephthalein excretion and at the same time an accumulation of urea nitrogen of the blood. Albumin, leukocytes and casts also appeared in the urines. This diminution in renal functional efficiency is demonstrable about the time of toxicity,

5. Hanzlik and Karsner: THE ARCHIVES INT. MED., 1917, **19**, 1016. Hanzlik, Scott and Thoburn: Ibid., 1030.

gradually becomes more severe, and finally (end of eighty to ninety hours) returns to its previous state. In almost every instance the impairment in renal function appeared before an increase in body weight was demonstrable. From this it seems that the renal factor plays an important rôle in the production of edema. It must be admitted that the part which tissues in general might play have not been absolutely excluded, for it is conceivable that in the beginning a marked diaphoresis could compensate for any accumulation of water.

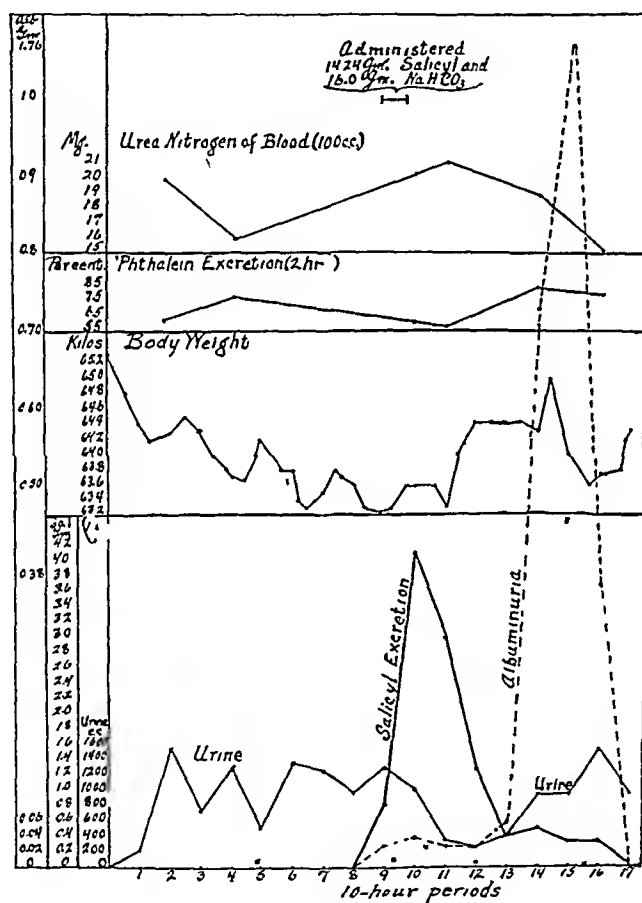


CHART 9.—Patient 30 (H. M.)

However, the following observation made by Sollmann and Pilcher⁶ tends to exclude direct action on the tissues, or at least so far as local edema is concerned, and therefore lends support to the renal factor. In connection with the study of a series of agents which give rise to endermic reactions characterized by hyperemia, swelling (wheal formation), etc., the application of sodium salicylate to the abraded skin does not give rise to local edema or urticaria such as is unmistakably produced by a large number of other drugs. The concentration used

6. Sollmann and Pilcher: Jour. Pharmacol. and Exper. Therap., 1917, 9, 309.

by Sollmann and Pilcher is much higher than the concentration of salicyl we have found in the blood even after the largest doses used by us. There is no reason to believe that salicyl would be more effective in smaller than in larger concentrations.

5. *Effect of the Administration of Sodium Bicarbonate.*—If the edema produced by the administration of salicylate is of the same nature as the salt edema of Widal, it could conceivably be accentuated by the administration of such a salt as sodium bicarbonate. It has also been observed that the administration of large doses of bicarbonate can cause edema. This also gave us the opportunity to test the claim that is made by some, namely, that edema is due to the production of acid, and the rational therapy indicated consists of the administration of alkali.

Sodium bicarbonate together with salicylate was administered to Patients 27, 28, 29 and 30. The urines remained alkaline throughout the experiment, or at least, during the increase in body weight. The phenomena observed under the bicarbonate-salicylate medication as compared with salicylate alone, remained practically unaltered. Of four patients studied, only one (29, Chart 8) failed to show an increase in body weight, owing to marked diaphoresis.

Sodium bicarbonate, therefore, has no demonstrable influence on the edema and diminution in renal functional efficiency, albuminuria, anuria, etc., produced by the administration of full therapeutic doses of salicylate.

CONCLUSIONS

1. The anuria produced by the administration of full therapeutic doses of salicylate is due to retention of water as indicated by an increase in body weight unless modified by diaphoresis.

2. This retention is demonstrable about twenty hours after the start of administration of the salicylate and persists until the salicyl excretion is completed, that is, about eighty hours (three and one-third days).

3. The retention occurs chiefly in the tissues, for no dilution of the blood is demonstrable by estimations of hemoglobin.

4. The edema is accompanied by a diminution in phenolsulphone-phthalein excretion together with an accumulation of urea nitrogen of the blood, and increased excretion of albumin, all of these elements reaching their previous levels with the disappearance of the edema.

5. There is, therefore, a diminution in renal functional efficiency, and since this generally makes its appearance before an actual increase in body weight is demonstrable (edema) and later coincides with it,

it seems that the renal factor plays an important rôle in the production of the edema.

6. These phenomena are not modified by the administration of sodium bicarbonate together with the salicylate, and in doses sufficient to maintain the urine alkaline.

We wish to express our thanks to Supt. C. H. McFarland and Dr. E. P. Carter, Chief of Medical Service, for extending the use of a special ward without which this and other investigations on salicylate would have been impossible; to Drs. Sheets and Kennedy, interns, and Messrs. T. W. Thoburn, M. E. Fulk and J. A. West of the third year class for various services rendered in connection with the work.

A STUDY OF POLIOMYELITIS

REPORT OF THE WORK OF THE MENINGITIS DIVISION OF THE RESEARCH
LABORATORY IN THE 1916 EPIDEMIC *

JOSEPHINE B. NEAL, M.D., HARRY L. ABRAMSON, M.D.
AND ASSOCIATES
NEW YORK

Since the work of the meningitis division was somewhat varied during the epidemic of poliomyelitis, it is convenient to describe it under three heads: Clinical Work and Laboratory Work, Pathologic Studies and Research Work.

The meningitis division was established by Dr. Park in 1910, as a division of the Department of Preventive Medicine, to afford to the physicians of New York City expert assistance in the diagnosis and treatment of meningitis. In connection with this work, a great variety of meningeal conditions have been studied. Among these were about seventy cases of poliomyelitis before the epidemic, most of them being either nonparalytic, or at least seen before the paralysis had developed. This had given us very good training in the correlation of the clinical picture and the spinal fluid findings necessary for the differential diagnosis of nonparalytic cases of poliomyelitis.

Early in June, 1916, it was noted that several cases of poliomyelitis occurred in Brooklyn, and that they were rather closely grouped. June 9, a letter was written to the Department of Communicable Diseases calling attention to this fact.

PART I. CLINICAL AND LABORATORY WORK

JOSEPHINE B. NEAL, M.D., PHOEBE L. DU BOIS, M.D., HENRY W. JACKSON, M.D.,
CHARLES H. NAMMACK, M.D., CAROLINE ROSENBERG, M.D., AND SAMUEL
PARNASS, M.D., WITH NATHAN NOVICK, HENRY W. ROGERS,
HERMAN GERBER, HELEN JONES, MIRIAM RAPHAEL, ROSE
RICHTER, LENA LEVINE AND DOROTHY COOPER
AS LABORATORY ASSISTANTS

Although effort has been made for a long time to differentiate poliomyelitis and establish it as a clinical entity, the first important con-

* Submitted for publication March 27, 1917.

* From the Department of Research, Bureau of Laboratories, Department of Health.

* The gold chlorid tests were carried out in Dr. George Draper's laboratory by Miss Georgia Cooper. We take pleasure in expressing our indebtedness to them for this valuable work.

* Preliminary report of the Quantitative Studies in Spinal Fluids was presented before the Society for Experimental Biology and Medicine, November, 1916. Compare Proc. Soc. Exper. Biol. and Med., 1916, 14, 26.

tribution to the study was a monograph published by Heine¹ in 1840.

Colmer,² in 1843, published an account of an epidemic of ten cases occurring in West Feliciana in 1841.

Strümpell,³ in 1884, published an article differentiating the cerebral type of the disease for the first time.

Medin,⁴ in 1890, published a study, which, with Heine's, ranks as a classic. Indeed, poliomyelitis is often called Heine-Medin's disease, from the epoch-making work done by them. Medin's work was based on epidemics in Sweden.

The first considerable epidemic in the United States occurred in Otter Creek Valley, Vt., in 1894, and was reported by Dr. Charles Caverly. About ten small epidemics were reported in the United States during the next twelve years.

In 1905 the first great epidemic occurred, over 2,000 cases being reported in Norway and Sweden. This was carefully studied by Wickman,⁵ whose work ranks in importance with that of Heine and Medin. He arranged an excellent classification, developed the epidemiology and pathology, demonstrated the contagious character of the disease, and described, for the first time, the nonparalytic or abortive form.

In 1907, a still larger epidemic, comprising about 3,000 cases, occurred in New York City.

In 1909, there was an outbreak of over 2,000 cases in Cuba.

In 1909 and 1910, epidemics appeared in various parts of the United States, District of Columbia, Iowa, Massachusetts, Minnesota, Indiana, Pennsylvania, Kansas, Maryland, New Hampshire, New York, Rhode Island, Virginia, Washington and Wisconsin: These varied in size from 200 to 500 cases, sometimes even more.

During this time important experimental studies, referred to elsewhere, were made both in this country and abroad.

A study of infantile paralysis in Massachusetts during 1910,⁶ reprinted from the *Monthly Bulletin* of the State Board of Health in 1912, includes clinical, epidemiologic and experimental work.

1. Heine, Jacob: Beobachtungen über Lähmungszustände der untern Extremitäten und deren Behandlungen, Stuttgart, 1840; Spinale Kinderlähmung, Stuttgart, 1860.

2. Colmer: Am. Jour. Med. Sc., 1843, **5**, 248.

3. Strümpell: Jahrb. f. Kinderh., 1884, **22**, 173.

4. Medin: Verhandl. d. Xth internat. Med. Cong., 1890, **2**, 6 Abt., p. 37.

5. Wickman, Ivan: Beiträge zur Kenntnis der Heine-Medinschen Krankheit, Berlin, 1907; Die akute Poliomyelitis, oder Heine-Medinsche Krankheit, Berlin, 1911.

6. Infantile Paralysis in Massachusetts During 1910. Monthly Bull. Massachusetts State Board of Health, 1912.

An excellent monograph, by Peabody, Draper and Dochez,⁷ in 1911, includes a careful clinical study, and also considerable laboratory and research work.

Kling and Leviditi⁸ published, in 1913, a very interesting epidemiologic study of the spread of the disease on two small islands, Djursö and Yxnö, where the movements of the people could be very closely followed. The progress of the disease either by direct contact or through carriers, was clearly shown.

F. E. Batten⁹ made a study of the epidemiology of the disease in England and gives in the Lumleian Lectures for 1916 a careful summary of the most important work done along various lines.

During the epidemic in New York in 1916, cases in which there was a disagreement between the department diagnosticians and the attending physicians were referred to us for diagnosis. This enabled us to study many atypical cases and to make some rather interesting differential diagnoses. From the middle of June until the middle of October, we were called on in 461 cases, in practically all of which poliomyelitis was suspected. Table 1 shows the final diagnoses, with a comparison of the patients seen and the diagnoses for the corresponding time in 1915.

TABLE 1.—COMPARISON OF DIAGNOSES IN 1915 AND 1916

	June 15 to Oct. 15, 1916	June 15 to Oct. 15, 1915
Anterior poliomyelitis	312	7
Anterior pollomyelitis, doubtful.....	29	
Tuberculous meningitis	29	16
Epidemic cerebrospinal meningitis.....	18	11
Other purulent meningitides..... ⁸	8	5
Acute syphilitic meningitis.....	1	0
Meningism	18	8
Other diseases	46	18

The increase shown in the number of other meningeal conditions indicates that these cases are incorrectly diagnosed at ordinary times when recourse is not had so freely to lumbar puncture.

The classification of a disease so protean in its manifestations as poliomyelitis is unsatisfactory. Wickman's classification is compre-

7. Peabody, Draper and Dochez: A Clinical Study of Acute Poliomyelitis. Pub. Rockefeller Inst. for Med. Research, 1911.

8. Kling and, Leviditi: Etudes sur la poliomyelitis Aigie Epidemique, Pub. de l'Inst. Pasteur, Paris, 1913.

9. Batten, F. E.: Acute Poliomyelitis (Lumleian Lectures, 1916), Brain, June, 1916, p. 115.

hensive, but is open to the objection that it is on both a clinical and a pathologic basis. It is also somewhat complex for general clinical use. It is as follows:

1. The spinal poliomyelitic form.
2. The form resembling Landry's paralysis.
3. The bulbar, or pontine.
4. The encephalitic.
5. The ataxic.
6. The polyneuritic (resembling neuritis).
7. The meningitic.
8. The abortive.

A classification on an anatomic basis and the degree of the lesion, is simple and quite easily used. We would suggest the following:

1. *Nonparalytic Type*.—Under this head are included cases in which the nerve cells are not sufficiently injured to produce paralysis. There may be weakness. Under this type should be classed meningitic cases and also those cases somewhat like tuberculous meningitis, but without motor disturbance, which we have called encephalitic, since the chief symptom seemed to be a depression of the sensorium. This is really only an accentuation of the drowsiness and stupor characteristic of the early stages. In these cases the motor cortical areas are not involved.

2. *Ataxic Type*.—The motor nerve cells are evidently not involved, but there is lack of coordination, ataxia, nystagmus, etc. In some cases an ataxic gait is the only sign of involvement of the central nervous system other than the sensory symptoms. The anatomic basis for this is proved by the postmortem findings of involvement of the cerebellum, Clark's column and the intervertebral ganglia. This type is very rare.

3. *Type with Cortical Paralysis*.—The upper motor neuron is affected, with resulting spastic paralysis. A true spastic paralysis is rare. More often are seen evidences of involvement of the upper motor neuron, increase of reflexes, or severe and prolonged convulsions. These convulsions are general and epileptic in character and may last for several hours.

4. *Type with Spinal or Subcortical Paralysis*.—The lower motor neuron is affected, with resulting flaccid paralysis. This is, of course, the most common form and the one first recognized and described.

Comparing this classification with that of Wickman, Group 4 corresponds with Wickman's Type 1, and includes his Types 2 and 3, since Type 2 is always an involvement of the lower motor neuron and Type 3 usually is. Group 3 corresponds with Wickman's Type 4, when actual lesions of the upper motor neuron are present; Group 2 with Type 5, Group 1 with Type 8, including those cases of Types 6

and 7 in which there is no paralysis, while cases of Types 6 and 7, in which paralysis is present, would fall under Group 3 or 4, depending on whether the upper or lower motor neuron is involved.

This classification is based on our experience during the epidemic, and cases were grouped under it after the epidemic was over. Had we been following it as the cases were studied, we could doubtless have made a more satisfactory grouping. Of course, cases sometimes fell in more than one group — Groups 2 and 4, most frequently.

The following is the classification of 512 cases:

Group 1.....	202	Mixed Groups:	
Group 2.....	4	Groups 2 and 4.....	3
Group 3.....	5	Groups 2 and 3.....	1
Group 4.....	296	Groups 3 and 4.....	1

Facial paralysis was rather common in this epidemic. Of 352 cases, there was facial paralysis alone in eighteen cases, combined with other paralysis in ten cases.

A manifestation of poliomyelitis, difficult to classify, is blindness.

Wickman⁵ says: "I may appropriately here mention that the optic nerve also is in rare cases affected." Tedeschi found complete blindness with optic atrophy in the left eye of a chronic case, and Wickman demonstrated optic neuritis in a recent case.

Three cases of blindness have been seen by the physicians of the meningitis division in poliomyelitis. In view of the rarity of the condition, a brief description of these cases may be of interest.

CASE 1.—E. M., aged 3 years; illness began Sept. 23, 1911, with symptoms characteristic of poliomyelitis. Partial paralysis of left arm and left side of face occurred, with left internal strabismus. About 70 c.c. of clear cerebrospinal fluid were withdrawn October 14. The changes were characteristic of poliomyelitis: marked increase in cells, 98 per cent. mononuclears; bacteriology negative; albumin and globulin ++. October 24, the general condition was better but the child was blind. Early in November the sight began to improve, and by the middle of December the child was perfectly well.

CASE 2.—I. C., aged 4 years 10 months. Illness began July 1, 1916, with paralysis of legs and neck and ptosis of left eyelid. The paralysis of the legs was spastic in type. Blindness developed. The patient died Sept. 11, 1916.

CASE 3.—R. J., aged 1 year. Illness began Aug. 31, 1916, with symptoms characteristic of poliomyelitis. There was no paralysis, but the child was blind (as nearly as could be determined) for three days. It made a complete recovery.

It is generally accepted that the most common cause of death is respiratory failure, due to the progressive paralysis of the muscles of respiration. The question of death occurring as a result of respiratory failure, or of cardiac failure due to the respiratory or cardiac centers being involved, has received but little consideration. Wickman, referring to the occasional occurrence of Cheyne-Stokes respiration, says that it is undoubtedly due to the respiratory center being affected. He

also mentions the possibility of the involvement of the vagus. Realizing that this question lies to a great extent in the realm of speculation, certain observations point to the desirability of giving it serious consideration. It is certainly possible to conceive from the pathologic findings that this condition may exist. Cases occur in which the only lesions are in the bulb and pons, there being no involvement of the cervical regions of the cord where the nerves controlling the muscles of respiration take their origin.

During the epidemic, death occurred suddenly, without signs of cardiac failure, in a few cases in which there was no paralysis of the muscles of respiration. In one case death occurred without evidence of paralysis, evidently from cardiac disturbance. For twenty-four hours preceding death there had been intervals of great irregularity of the heart, though the heart itself, from the physical examination, was apparently normal. Such a condition might conceivably arise from a progressive involvement of the vagus center in the medulla.

In several instances there was evidence of a transient involvement of the cardiac or respiratory centers, as shown by marked irregularity of the heart or respiration, which cleared up completely. As a specific example of a fatal case of this kind, the following may be cited:

I. F., aged 2 years. The illness began July 26, 1916, with facial paralysis. The spinal fluid showed pathologic changes, such as are commonly found in poliomyelitis. Death occurred July 31, no signs of paralysis of the respiratory muscles having developed. The microscopic pathology of this case showed the lesions of poliomyelitis present only in the pons and bulb.

The classification of this particular type is difficult. Of course the lesions occur in the pons and bulb. These cases, especially when fatal, are usually associated with paralysis of the cranial nerves—the facial or glossopharyngeal, abducens, etc. These are lower motor neuron lesions and are classified by us under Group 4. We are at a loss to know how to place a lesion of the vital centers.

The existence of this type of lesion does not seem to have been very clearly differentiated in the past. Even Wickman refers to paralysis of the respiratory muscles and lesions of the respiratory center without clearly distinguishing the conditions. Doubtless further study will throw more light on the clinical and pathologic side of this question.

It is maintained by some authorities that poliomyelitis is essentially a general infection, and that symptoms of its effects on the central nervous system are entirely secondary in nature, when not absent altogether. It has even been suggested that paralytic cases may be in reality the atypical ones. Those holding this view would, in times of epidemics, diagnose as poliomyelitis cases presenting merely respiratory or gastro-intestinal symptoms, particularly if a case of frank

paralysis exists in the same family at the time. When we consider the prevalence of gastro-intestinal disturbances in children, more especially during the summer season, such a conclusion is hardly tenable, unless corroborated by characteristic findings in the spinal fluid.

Personal experience inclines us to believe that the changes in the spinal fluid commonly accepted as diagnostic of poliomyelitis do not exist independently of some definite clinical manifestation of involvement of the central nervous system. It does not seem possible that a disease accompanied by an inflammatory reaction in the central nervous system and meninges of sufficient severity to produce changes in the spinal fluid could fail at the same time to afford some clinical evidences of nerve involvement. Therefore, in the past, we have made it a rule to consider the possibility of poliomyelitis, and to perform lumbar puncture only in those cases presenting symptoms referable to the nervous system, such as hyperesthesia, Kernig's or the spinal sign, altered reflexes, stiffness of the neck, Macewen's sign, etc. In the absence of these signs and in the presence of a normal spinal fluid, we have always definitely excluded poliomyelitis.

When none of these signs was present we have usually considered a lumbar puncture unjustifiable. In the few cases in which we have performed it, the fluids have been normal.

During the recent epidemic we performed punctures irrespective of our own opinion as to the diagnosis, to clear up doubtful cases, and the results have justified our earlier views.

At the other extreme from those regarding poliomyelitis as a general infection and the paralytic cases as atypical, are physicians, few in number to be sure, who regard as suffering from poliomyelitis, only those patients with a frank paralysis. The following reasons seem to prove quite conclusively the existence of the nonparalytic type:

1. The filtered washings of the nose and throat of such patients, in a considerable number of instances, have produced typical poliomyelitis in monkeys.
2. The findings in the spinal fluid in these cases are identical with the findings in poliomyelitis with paralysis.
3. The findings in the spinal fluids in cases of meningism in gastro-enteritis, pneumonia, the exanthems, etc., are usually quite distinctly different.
4. The serum from nonparalytic patients possesses the same neutralizing power as the serum from paralyzed patients.

Symptoms of Onset.—The initial symptoms are much the same in all types of the disease, and they may be quite as severe in the non-paralytic as in the paralytic forms. There is a type of onset described

by Kling, Leviditi and others, which we have sometimes observed. In this, the disease is ushered in by somewhat indefinite symptoms of an intestinal or anginal nature. A remission of from one to several days then occurs, to be followed by a return of all symptoms, and usually by an accompanying paralysis.

While the onset may rarely be insidious, in the vast majority of cases it is very abrupt. Fever is probably the most constant, as well as usually the first, symptom. As a rule, it is high and of comparatively short duration, falling by crisis or by lysis. Next to fever, the most frequent symptom is a pronounced hyperesthesia or diffuse tenderness over the whole body. This is, perhaps, most marked in the legs and along the spine. There is also a decided drowsiness and the patient manifests great irritability when disturbed. Headache and vomiting are common. Constipation or diarrhea may be present; in our own experience, the former being more frequent. Retention of urine sometimes occurs, and this possibility should be constantly borne in mind. Convulsions, twitchings of groups of muscles, delirium, and pains in the neck, back, joints and limbs are other symptoms which may appear. Meningeal symptoms are pronounced in a fairly large portion of cases. These are, anteroposterior stiffness of the neck; Kernig's sign; MacEwen's sign, or change in the percussion note over the lateral ventricles, due to distention with fluid. The reflexes may be exaggerated, but usually they are diminished or abolished. They are frequently unequal. The pupillary reflex is, as a rule, retained. Following these symptoms, paralysis may develop, most commonly appearing about the second day, though it may be delayed as late as the second week.

While occasional references to herpes zoster associated with poliomyelitis are noted in the literature, it would seem that the association must be accidental, or else especially characteristic of certain epidemics. In this epidemic no instances were seen by us of this manifestation, nor is there any record, to our knowledge, of herpes zoster occurring in experimental poliomyelitis. If it were due to the virus of poliomyelitis, it would seem that this manifestation would occur occasionally, at least, in monkeys artificially infected, inasmuch as in these cases the posterior root ganglia invariably show the typical pathologic lesions.

Differential Diagnosis.—In the first twenty-four to forty-eight hours after its onset, poliomyelitis must be differentiated from the early stages of epidemic meningitis, or mild purulent meningitis, and also from a meningism accompanying pneumonia or other infection. The clinical pictures presented by the diseases mentioned are quite similar, and it is in distinguishing between them that the examination of the spinal fluid affords us the most reliable information.

When seen a week or more after onset, cases of poliomyelitis, especially if presenting cerebral symptoms, must be distinguished from tuberculous meningitis.

Though the differential diagnosis of typical cases of early poliomyelitis and early purulent meningitis would be fairly easy, many cases are atypical.

While epidemics of poliomyelitis usually occur in hot weather, and epidemics of meningitis in the winter or spring, sporadic cases of either occur at any time.

A history of a gastro-enteritis or an anginal attack three or four days prior to the onset, is much more suggestive of poliomyelitis than of meningitis. A history of an otitis media, an operation on the nose or throat, or a severe injury to the head with possible fracture of the skull, makes one suspect a meningitis, due most likely to the pneumococcus or streptococcus.

The temperature in poliomyelitis is usually higher at the onset, but falls more quickly than in meningitis.

There is usually greater hyperesthesia in poliomyelitis; the reflexes are more likely to be unequal and the pupillary reflexes are very seldom lost.

In meningitis there is usually greater stiffness of the neck and a more pronounced Kernig. Delirium is far more common than in poliomyelitis. A hemorrhagic eruption, or herpes, if present, strongly suggests meningitis.

The differential diagnosis between poliomyelitis and meningism is much more difficult until the underlying cause of the meningism develops. Even then we may wonder if the pneumonia or gastro-enteritis, etc., may not be a complication of the poliomyelitis.

In differentiating poliomyelitis and tuberculous meningitis, one should remember that while the onset is usually sudden in poliomyelitis and gradual in tuberculous meningitis, some few cases of poliomyelitis give a history of a gradual onset, and occasionally tuberculous meningitis begins abruptly. In the cases of poliomyelitis resembling tuberculous meningitis, the stupor is usually not so profound, there is no projectile vomiting, the pulse is usually regular, and the progress of the case after the first week or ten days is generally toward recovery.

Occasionally in tuberculous meningitis a paralysis develops of the muscles of the eye. Sometimes other paralyzes develop, as of the face or arms. These are usually transitory.

In all these conditions the differential diagnosis depends greatly on the spinal fluid findings.

An attempt was made to follow up cases to determine how infectious poliomyelitis is, or how much natural immunity children have, by

studying the number of secondary cases developing in families, a member of which was known to have the disease:

In following up 360 cases it was found that in 198 instances there were other children in the family who were, therefore, directly exposed to the disease. The children thus directly exposed numbered 443 and of these twenty-eight, or 6.3 per cent., developed the disease. This is in accordance with work done by Emerson¹⁰ in Massachusetts and Hill¹⁰ in Minnesota, in 1909. The distribution by families was as shown in Table 2.

TABLE 2.—OCCURRENCE IN CONTACTS IN SAME FAMILY

Number of Children in Family	Number of Families	Children Developing Disease	Number of Children in Family	Number of Families	Children Developing Disease
2	72	13	6	9	1
3*	60*	9*	7	5	1
4	31	4	8	1	0
5	18	0			

* Among these families in two instances all three children developed the disease. These were the only instances in which more than two children were sick.

Table 2 shows that a relatively large number of children must have a considerable natural immunity to the disease, since, when exposed so closely to poliomyelitis, so few developed it.

Outcome of Cases.—The results at the end of two months in 507 cases studied were as follows:

Class 1 (Nonparalytic): Of 202 cases, 173 recovered completely; 29 had weakness remaining.

Class 2 (Ataxic): Of 4 cases, 4 patients recovered.

Class 3 (Cortical or upper motor neuron paralysis): Of 5 cases, 5 patients died.

Class 4 (Spinal or lower motor neuron paralysis): Of 296 cases, 32 recovered completely; 32 recovered with weakness; 130 had paralysis remaining after two months; 102 died.

The cases under Classes 2 and 3, of course, are too few to make it possible to draw conclusions.

It will be noticed that of these 507 cases, 202, or 40 per cent., were nonparalytic. We saw a relatively large proportion of nonparalytic cases, since that type of case was the one in which there was most frequently a difference of opinion, and which we were therefore called to see.

10. Infantile Paralysis in Massachusetts in 1909. Bulletin Massachusetts State Board of Health, 1909.

Of Class 4, the spinal or lower motor neuron type, 130, or 67 per cent. of the 194 surviving, showed a residual paralysis at the end of two months.

Treatment.—In the minds of the general public, and of most physicians, there exists a close analogy between the use of serum in epidemic meningitis and in poliomyelitis, and its success in the former has influenced them to have faith in its success in the latter. The pathology of the two conditions, however, is quite different. In acute purulent meningitis the process is limited almost entirely to the meninges, the brain and cord substance being little, if at all, involved, though there may be some secondary congestion. In poliomyelitis, however, the pathologic picture is reversed. Here, the brain and cord substance is mainly involved, whereas the inflammation in the meninges is secondary. Injecting a foreign substance into the slightly inflamed meninges sets up, in most cases, an acute aseptic meningitis, as is shown by changes in the spinal fluid, and clinically, by the increased temperature, rigidity of the neck and other signs of meningeal irritation. It is possible that this increased inflammatory reaction may tend to accentuate indirectly the inflammatory changes already existing in the subjacent substance of the brain and cord. That this reaction may be harmful is borne out by the results of animal experimentation, which are described in another place. On the other hand, certain workers feel that a beneficial phagocytosis may result from the increased leukocytes. In meningitis, however, the injection of serum into actively inflamed meninges is not followed by an increase in the inflammatory reaction, as is evidenced by the clearing up of the fluid and the amelioration of the clinical symptoms in favorable cases.

It seems to us, therefore, that the setting up of an acute aseptic meningitis may be harmful. As to its specific neutralizing power, this would have to be exerted very speedily, since the damage is so often done within forty-eight to seventy-two hours after the onset of symptoms. Such a speedy effect is not seen in the case of antimeningitis serum, tetanus antitoxin, etc.

The unanimous opinion of the physicians of the meningitis division is voiced in the preceding discussion.

The members of the meningitis division did not administer serum in a very large number of cases, because the early experiences were so discouraging that they did not feel that they could urge its administration. The reaction following the introduction in the cases of the patients who survived was often so severe that it was felt that it might have been an injurious factor in some instances.

They feel that the best results of treatment in early cases is obtained by complete rest, with lumbar puncture for the relief of signs of men-

ingeal irritation. Symptomatic and hygienic treatment should, of course, be carried out. The importance of rest cannot be too strongly emphasized. That form of treatment would need to be of definite and well-established value that can justify the frequent disturbance of a desperately sick child for the administration of treatment intraspinally.

THE CEREBROSPINAL FLUID IN POLIOMYELITIS

In 1908, Dr. Martha Wollstein¹¹ published a biologic study of the cerebrospinal fluid in anterior poliomyelitis. This included bacteriologic and complement fixation work, rather than cytologic and chemical studies, and refers in detail to still earlier work along those lines.

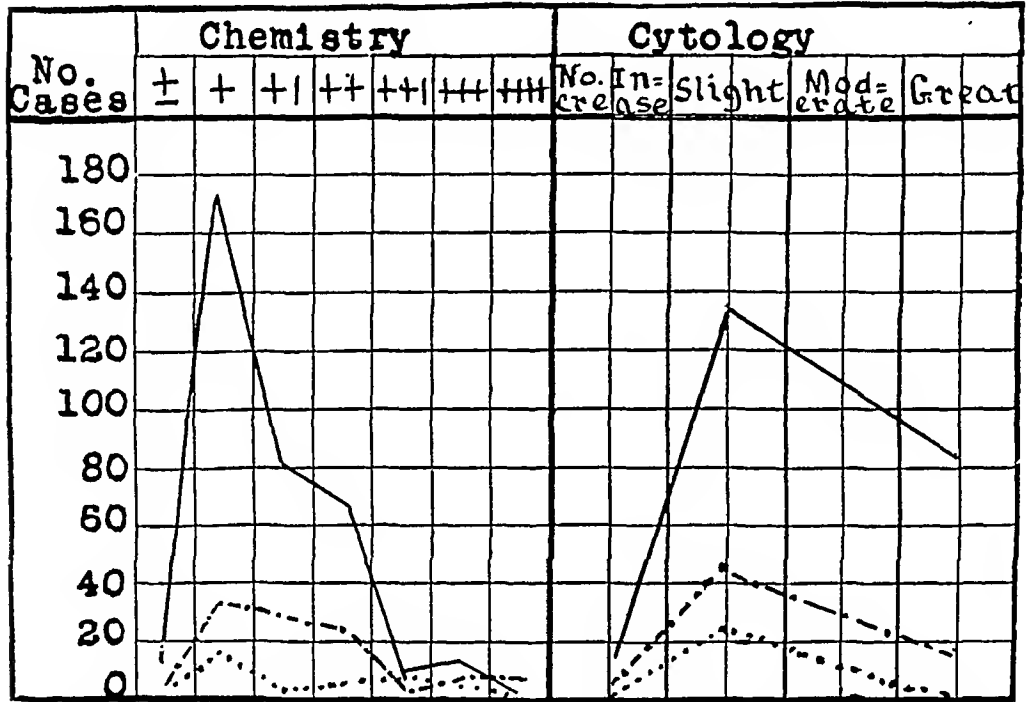


CHART 1.—Showing the variations in the chemistry and cytology of the cerebrospinal fluid in poliomyelitis. Upper curve ———, first week; middle curve — — — — —, second week; lower curve, subsequent weeks. An idea may be gained from these curves as to the significance of the laboratory findings in the first and second and subsequent weeks. In the cytology the curves are nearly parallel, showing no tendency for greater cytology at any one time than another. There were relatively more cases with low chemical findings in the first week than in the later periods, but low chemical findings predominated in all three periods.

Gay and Lucas,¹² in 1910, published one of the earliest and most important studies, embracing cytologic and chemical work on the spinal fluid, both from human cases and from the experimental disease in monkeys.

11. Wollstein: Jour. Exper. Med., 1908, 10, 476.
12. Gay and Lucas: THE ARCHIVES INT. MED., 1910, 6, 330.

The spinal fluid was carefully studied in the monograph published by Peabody, Draper and Dochetz,⁷ already referred to, and this work was continued by Fraser.¹³

PART II. PATHOLOGIC STUDIES

HARRY L. ABRAMSON, M.D.

The routine laboratory work consisted in the examination of spinal fluids, including those withdrawn by the personnel of the meningitis division, those sent in by private physicians, and those withdrawn at the Willard Parker Hospital and at the Kingston Avenue Hospital. To take care of the fluids at the latter place, it was necessary to establish a laboratory there.

The examination of the spinal fluid is the most valuable laboratory aid in the diagnosis of poliomyelitis, but even here there are no pathognomonic findings, as, for example, the infecting organism in a purulent or a tuberculous meningitis. It is by ruling out other conditions that it is of value, and it is of the greatest service only when correlated with a careful clinical study of the case.

The spinal fluid in poliomyelitis is usually increased in amount and escapes under pressure. It is clear or slightly hazy in appearance, and sometimes shows the fibrin web formation which was formerly considered pathognomonic of tuberculous meningitis.

In poliomyelitis, the spinal fluid shows evidence of an inflammatory reaction — there is a varying increase in the cells and in the albumin and globulin. In a few cases these evidences of an inflammatory reaction are well marked; in most cases they are moderate; while in a few cases, at the other extreme, they are so slight and the fluid so nearly approaches normal that it is difficult to make a definite statement in regard to the findings. The reduction of Fehling's solution in these fluids is practically always as prompt as in normal fluids.

The technic which we employ in examining spinal fluids is as follows:

Technic.—All clear or slightly cloudy fluids in approximately the same amounts are centrifuged for an hour at high speed. From the sediment spreads are made, taking care to use as nearly as possible, the same area on the different slides. The sediments of clear fluids are stained by the Ziehl-Nielsen method for the tubercle bacillus; the sediments of slightly cloudy fluids for both the tubercle bacillus and by the Gram method. From this stained sediment we can estimate the increase in cells as slight, moderate, great, or very great. We do not feel that the exact number of cells has more than an academic interest. Indeed, as the cell count was the first study to be made in spinal fluids, an undue emphasis has been placed in the past on finding out the presumably exact number of cells, and many workers having made this deter-

13. Fraser, F. R.: A Study of the Cerebrospinal Fluid in Acute Poliomyelitis. Jour. Exper. Med., 1913, 18, 242.

mination, have been content to rest on it, omitting other investigations at least equally important. Moreover, the attempt to determine the exact number of cells in the spinal fluid, even in the hands of experienced laboratory workers, is not so simple or accurate a problem as doing a white cell count in the blood. This was borne out by our experience during the summer, when the same fluid examined under the same conditions by different workers gave widely varying results. This is to be accounted for by the presence of a few red blood cells that are often found, even in the clearest fluids. It is difficult to get rid of these red blood cells, as only a small amount of diluting fluid can be used. Detritus also may be mistaken for cells.

Certain of our workers who have had experience with both methods have become convinced that, on the whole, the smear method is the more reliable. A fixed and stained preparation leaves no doubt as to the exact character of sediment. We made a fair number of cell counts in connection with the smear method, and we find that, on the whole, the two methods check up very well. Indeed, there were several striking instances of the greater reliability of the smear method.

The cell count in poliomyelitis and tuberculous meningitis, while on the average higher in the latter, overlaps for so wide a range as to render the differential diagnosis by this point most unreliable. Moreover, while some claims to the contrary have been made, it is not our experience that the number of cells in poliomyelitis fluids bears any relation to the prognosis of the case, as is shown in Tables 5 and 6. From these stained sediments we also estimate the percentage of mononuclears and polymorphonuclears, and note the presence of endothelioid and polyform cells. The presence or absence of bacteria was also noted. Cultures were made from all specimens. In the case of uncontaminated poliomyelitis fluids they have been uniformly negative.

The chemical tests that we use are the nitric acid ring test for albumin, and the Noguchi butyric acid test for globulin. The albumin and globulin practically always run parallel, but they serve as a check on each other. The small amount of albumin and globulin present in normal fluids is marked \pm . The signs +, +1, ++, +++1, +++, +++++, represent increasing amounts and serve as a rough quantitative estimation. The presence of glucose is tested by using an equal amount of Fehling's solution and spinal fluid, and it is marked with regard to the speed and the amount of reduction as —, +, +1, ++, +++. The globulin reaction and the reduction of Fehling's solution should not be read for at least half an hour.

Findings.—Taking up these points somewhat in detail, let us first consider the cytology. The increase in cells varies very greatly, both in different cases and in the stage at which the puncture is done. Our counts have varied from slightly above normal, 15 or 20, to 1,200. The counts tend to fall off after the first week, and by the end of the second week have usually fallen nearly to normal. That this does not always happen is shown in Table 1.

The cells usually show a preponderance of mononuclears, but in a few instances there is over 50 per cent. of polymorphonuclears. It has been stated that early in the disease there is an excess of polymorphonuclears, which later is replaced by mononuclears. A large number of early fluids, on the second, third and fourth days, were examined by us. Out of a series of 2,000 fluids, many of them early, the polymorphonuclears predominated in only thirty-nine cases as follows: 4 on the second day; 6 on the third day; 1 on the fourth day; 5 on the fifth day;

3 on the sixth day; 7 on the seventh day and so on as late as the twenty-first and twenty-seventh days. We feel, therefore, that the polymorphonuclears represent a special type of reaction — not a stage of the disease. Often, even in fresh fluids, the cells are so degenerated that it is difficult to classify them. There are large mononuclear cells, endothelioid in type, that seem to us to occur more frequently in poliomyelitis than in other conditions. The so-called polyform cells are also found.

The albumin and globulin are usually slightly to moderately increased.

Fehling's solution, as has been stated before, is practically always well reduced. The fluids that show a poorer reduction are usually those with the larger amount of albumin and globulin.

Differential Diagnosis of Poliomyelitis Fluids.—The slightly cloudy fluids must be differentiated from those of early cases of purulent meningitis and from the slightly cloudy fluid that occasionally occurs in tuberculous meningitis. The clear, or practically clear, fluids must be differentiated from rare, early cases of purulent meningitis, tuberculous meningitis, syphilis of the central nervous system, especially acute syphilitic meningitis, and meningism. Other rarer conditions might be mentioned, but these are the most important.

In early cases of purulent meningitis the spinal fluid shows a varying degree of cloudiness, except in very rare instances, when it may be clear. A greater increase in albumin and globulin is usually found than occurs in poliomyelitis, with a poorer reduction of Fehling's solution. The cells in the fluids of purulent meningitis are 90 per cent. or more polymorphonuclears, and the etiologic organism is always found except in the mildest cases, or in cases of basilar meningitis when the puncture is done late. In certain mild cases of meningitis — probably of the epidemic variety — the meningococci may never be positively demonstrated in the fluid. In purulent meningitis, due to other organisms, these practically always appear later. In two instances we have seen clear fluids from early cases of epidemic meningitis of about eighteen hours' standing. Although the cellular reaction was so slight, the meningococcus was demonstrated to be present in the fluid by smear and culture.

The fluid in tuberculous meningitis most nearly resembles that of poliomyelitis. It is practically always clear, with a cellular increase consisting largely of mononuclears, though in very acute cases it may be distinctly cloudy, with an excess of polymorphonuclears. Fortunately, in these cases, the tubercle bacillus is usually easy to demonstrate. The number of cells per cubic millimeter is usually greater than in poliomyelitis; the increase in albumin and globulin is more marked, and the reduction of Fehling's solution is not so good.

TABLE 3.—RELATION OF DAY OF PUNCTURE TO LABORATORY FINDINGS

Day of Puncture	Cytology					Chemistry							
	No. of Fluids	No Increase	Slight	Moderate	Great	±	+	+1	++	+++	++++	+++++	+++++
1	2	...	1	...	1	..	1	1					
2	52	2	22	17	11	2	30	13	3	2	1	1	
3	63	2	20	21	20	3	29	14	13	1	2	1	
4	71	4	29	22	16	2	37	17	9	1	5		
5	77	3	24	30	20	2	34	14	20	4	2	1	
6	50	3	25	11	11	1	28	11	8	..	2		
7	39	2	16	13	8	1	16	12	7	1	2		
8	27	...	12	8	7	1	10	5	6	1	4		
9	20	...	8	8	4	1	12	4	2	1			
10	15	2	7	6	..	1	3	4	4	3	
11	9	1	3	2	3	..	1	5	2	..	1		
12	15	...	10	3	2	1	5	3	1	1	3	1	
13	11	1	4	4	2	1	3	1	3	1	2		
14	6	1	3	1	1	2	2	2			
15	5	...	3	2	1	1	3				
16	2	...	2	1	1	
17	5	...	5	4	..	1				
18	1	1	1			
19	2	...	1	1	1	..	1				
20	2	...	2	1	1			
21	6	...	2	3	1	..	2	1	2	1			
23	1	1	1					
24	1	...	1	1							
25	1	...	1	1					
27	1	...	1	1						
28	1	...	1	1					
30	4	...	2	1	1	..	1	2	..	1			
35	3	2	1	1	..	1	1			
40	2	...	1	1	2						
41	1	...	1	1			
43	1	...	1	1						
48	1	1	1						
50	3	...	2	1	2	1					
	500	23	211	153	103	17	227	114	89	21	24	8	

The great majority of cases show a slight or moderate increase in the cells and a + or +1 chemistry. The pathologic changes in the fluid both as to cytology and chemistry persist longer than has commonly been believed.

In rare instances, when clinical signs are confusing and when the results of the cellular examination and chemical analysis are indefinite, and it is impossible to demonstrate the tubercle bacillus in the fluid, a positive diagnosis must wait on the results of animal inoculation.

The fluid of an acute syphilitic meningitis closely resembles the fluid of poliomyelitis, and the clinical signs are also confusing. The Wassermann reaction is the best method of differentiating the two conditions. Of course, a positive Wassermann would not rule out poliomyelitis in an old syphilitic condition, but this, combined with the clinical conditions and the progress of the case, makes one reasonably sure of the diagnosis. It was suggested at first that the products of degeneration present in the spinal fluid of poliomyelitis cases might give a nonspecific Wassermann reaction. Tests in about 350 cases were made by Miss May Wilson, and have indicated that this is not true.

TABLE 4.—RELATION OF CYTOLOGY TO CHEMICAL FINDINGS

Cytology		Albumin and Globulin						
		±	+	+1	++	+++	++++	+++++
No Increase.....	23	1	12	7	3	0	0	0
Slight.....	211	9	105	39	35	9	11	3
Moderate.....	158	5	73	35	31	5	6	3
Great.....	108	2	37	33	20	7	7	2
	500	17	227	114	89	21	24	8

The chemistry does not run parallel with the cytology, as is clearly shown in the table.

TABLE 5.—RELATION OF CONDITION AT THE TIME OF PUNCTURE TO FINDINGS

		Cytology				Chemistry						
		No Increase	Slight	Moderate	Great	±	+	+1	++	+++	++++	+++++
No paralysis	41	5	15	15	6	2	26	6	3	1	1	2
With weakness	261	11	102	83	65	12	121	54	50	13	8	3
With paralysis	198	7	94	60	37	3	80	54	36	7	15	3
	500	23	211	158	108	17	227	114	89	21	24	8

A majority of cases had slight increase in cells. A majority of cases had one plus chemistry. There is no relation between the paralytic condition and the spinal fluid findings, either as regards cytology or chemistry.

The fluid of meningism is clear, increased in amount, and practically always normal in character. The few exceptions to this that we have found in a large number of cases have fallen mainly into three groups — fluids from patients with prolonged and severe convulsions; fluids in severe whooping cough, and fluids removed just prior to death. In these cases there have sometimes occurred an increase in cells, or in albumin and globulin, or in both. In convulsions, there is probably edema, in whooping cough minute hemorrhages, and, just before death, circulatory changes, to account for it.

Lange's colloidal gold test has been used to some extent by workers to whom we have given specimens of fluid. This is discussed later.

Two rare types of spinal fluids sometimes occur in poliomyelitis when the hemorrhagic process has been more than usually severe. The first of these is of true hemorrhagic character, the red blood cells being evenly diffused throughout the fluid. When collected in successive tubes, the specimens are all homogeneous, showing no change in the

TABLE 6.—RELATION OF CELL INCREASE TO OUTCOME; CONDITION AFTER APPROXIMATELY EIGHT WEEKS

		Cytology		Complete Recovery	Weakness or Recovering Paralysis	Paralyzed	Dead	Mortality Per Cent.
Lumbar puncture in first week of illness.....	354	No increase...	16	9	0	4	3	19
		Slight.....	137	57	20	34	26	19
		Moderate.....	114	50	10	25	29	25
		Great.....	87	35	11	23	18	20
Second week.....	103	No increase...	5	0	1	2	2	40
		Slight.....	47	18	9	15	5	10
		Moderate.....	32	15	2	4	11	34.
		Great.....	19	7	4	5	3	16
After second week...	43	No increase...	2	1	1	0	0	0
		Slight.....	27	10	1	12	4	15
		Moderate.....	12	3	2	6	1	8
		Great.....	2	2	0	0	0	0
500			500	207	61	130	102	

In the first and second weeks the cases with a moderate increase (from about seventy-five cells to 150 cells) had a higher mortality than the cases with a slight increase, or the cases with a great increase. It would be safe to conclude from this that a high cell count does not carry with it a bad prognosis.

intensity of the hemorrhage. This serves to differentiate the fluid from bloody fluids obtained by the accidental puncture of a vein.

Evidence of an older hemorrhage occurs in the second of these rarer fluids, which, having a characteristic yellow color and coagulating spontaneously, illustrates the so-called syndrome of Froin. These fluids occur in other conditions, and are, therefore, not pathognomonic of poliomyelitis.

While about 2,000 poliomyelitis fluids were examined, only 500 were carefully studied. Five hundred is accepted by statisticians as a number furnishing absolutely reliable data from which to draw conclusions. It seemed better, therefore, to take this number and make careful studies, combining clinical data with the spinal fluid findings, rather than to try to use a larger number and study the data less thoroughly.

TABLE 7.—RELATION OF CHEMISTRY TO OUTCOME

		Chemistry	Complete Recovery	Weakness	Paralyzed	Died	Mortality, per Cent.
First week	354	+	6	1	1	3	27
		+	91	18	37	29	16
		+1	27	14	21	20	24
		++	19	6	20	15	25
		++1	1	1	4	3	33
		+++	2	1	6	5	35
		++++	1	1	0	1	33
			147	42	89	76	
Second week	103	±	4	0	0	1	20
		+	13	5	7	9	26
		+1	6	4	8	6	25
		++	9	4	5	2	10
		++1	3	0	3	0	0
		+++	3	1	3	3	30
		++++	2	0	0	2	50
			40	14	26	23	
Third week	43	±	0	0	0	1	100
		+	9	1	7	1	5½
		+1	2	2	4	0	0
		++	6	2	1	0	0
		++1	3	0	2	1	16
		+++	0	0	0	0	0
		++++	0	0	1	0	0
			20	5	15	3	
	500		207	61	130	102	

Of course with the smaller numbers, the mortality percentage means practically nothing. In the first week, cases with a + chemistry did better than those with a higher chemistry, but this did not hold in the second week. It would seem safe to conclude from this that the chemistry has no very definite prognostic value.

TABLE 8.—RELATION OF CONDITION AT TIME OF PUNCTURE TO OUTCOME;
CONDITION AFTER APPROXIMATELY EIGHT WEEKS

Lumbar Puncture in		Condition at Time of Puncture		Complete Recovery	Weakness or Recovering Paralysis	Paralysis	Dead
First week of illness.....	354	No signs of paralysis.....	31	25	2	1	3
		Weakness or other marked symptoms....	197	108	25	30	34
		Paralyzed in some part.....	126	18	14	55	39
Second week...	103	No signs.....	8	6	1	1	0
		Weakness.....	48	28	8	7	5
		Paralyzed.....	47	6	7	18	16
After second week.....	43	No signs.....	2	2	0	0	0
		Weakness.....	16	11	1	1	3
		Paralyzed.....	25	3	3	17	2
	500		500	207	61	130	102

This table shows that while, after the first week, as is obvious, the chances of recovery are better, nevertheless, even later, it is quite impossible to make a prognosis that is at all definite.

PART III. RESEARCH WORK

1. GOLD CHLORID TEST.

J. B. NEAL, M.D., AND H. JONES

Zsigmondy, following an exhaustive study of the subject of the "coagulating" action of electrolytes on metallic colloidal solutions, was able to find a definite measure of the protective action of certain colloids, especially proteins, on the precipitation of gold suspensions by sodium chlorid. The degree of protection was specific for each protein he examined.

By using this general method he was unable to distinguish between syphilitic and normal serums.

Lange proceeded further and found that normal spinal fluids, suitably diluted with a 0.4 per cent. solution of sodium chlorid, cause no alkalination in suitable solutions of colloidal gold, and abnormal spinal fluids cause partial or complete precipitation of colloidal gold, with resultant color changes occurring in curves, which tend to be almost specific for certain diseases, particularly those of syphilitic origin.

This specificity is characterized by maximal color changes within dilution zones.

TABLE 9.—SUMMARY OF 500 CASES

TABLE 9.—SUMMARY OF 500 CASES															
Types of Cases		Cytology				Chemistry						Outcome			
		No In-crease	Slight	Mod-erate	Great	±	+	+1	++	+++	++++	Complete Recovery	Weak Paral- yzed	Died	
Class 1	No paralysis.....	202	77	65	46	12	103	36	35	8	5	3	173	29	
Class 4	Flaccid paralysis.....	296	133	92	62	5	123	77	51	13	19	5	32	32	
Class 2	Ataxic.....	2	1	1	1	1	2	102	
		500	211	153	108	17	227	114	89	21	24	8	207	61	130
The cases were about evenly divided between two types—paralytic and nonparalytic.															
Both types in the majority of cases had slight increase in the paralysed tissue.															
The paralysed tissue in the majority of cases had slight increase in the paralysed tissue.															

The cases were about evenly divided between two types—paralytic and nonparalytic. Both types in the majority of cases had slight increase and one plus chemistry. The paralyzed type in the majority of cases remained paralyzed. The nonparalyzed type in the majority of cases recovered. Out of 500 cases, in most there was a slight to moderate increase; in most there was one and one-half chemistry; in most there was recovery. The percentage of those that made complete recovery after being paralyzed is 12.2. The complete recovery among those not paralyzed is 76.2 per cent.

Fluids from different types of meningitis give reactions with greatest intensity in higher dilutions.

Paretic fluids cause complete flocculation in the first four to six dilutions.

Tabes and cerebrospinal lues give maximal reactions in fourth to fifth dilutions.

We have Lange results on 114 poliomyelitis fluids (Table 10).

Colloidal Gold Test.—Into the first of eleven test tubes put 0.9 c.c. of fresh, sterile 0.4 per cent. sodium chlorid solution. Into each of the remaining tubes put 0.5 c.c. of the 0.4 per cent. sodium chlorid solution. Add to the first tube 0.1 c.c. of the spinal fluid to be tested. Mix well.

Transfer 0.5 c.c. of the resultant 1 to 10 dilution of spinal fluid to the second tube. Mix well.

Transfer 0.5 c.c. of the resultant 1 to 20 dilution of spinal fluid to the third tube. Mix well.

Proceed in this manner up to and including the eleventh tube.

By this method a series of dilutions of spinal fluid is secured, in geometrical progression, ranging from 1 to 10, to 1 to 5,120.

Now add to each tube 2.5 c.c. of colloidal gold solution.

Shake each tube thoroughly and do not read for twelve hours.

The various types of color changes seen in a positive gold reaction are indicated by numerals as follows:

Complete decolorization.....	5	Lilac or purple.....	2
Pale blue.....	4	Red-blue	1
Blue	3	Brilliant red-orange.....	0

A normal fluid would remain brilliant red-orange color and would, therefore, read 00000000000 or 1110000000.

A poliomyelitis fluid would remain brilliant red-orange color in the first two tubes, slightly bluish in the third, purple in the fourth tube, and again bluish in the fifth, returning to normal red-orange in the sixth tube, and would, therefore, read 00123000000 — being a weak syphilitic curve.

A meningitis fluid unchanged in the first two tubes and ranging from this to colorless in the ninth tube and back to original in the eleventh tube, would read 00011245210.

Charts showing these typical reactions and readings are appended.¹⁴

Chart 2 shows the three curves of paretic, meningitic and syphilitic spinal fluids, according to the Bulletin of the Johns Hopkins Hospital, referred to.

Charts 3 to 8 show various poliomyelitis curves of fluids of our own.

Chart 9 is the composite of 3 to 8, giving the average curve for 114 fluids.

Our own fluids fell into six different groups, depending roughly on the albumin and globulin content. These are shown in Charts 3 to 8, while Chart 9 is a composite.

14. These charts are taken from Bull. 298, Johns Hopkins Hosp., 1915, 26.

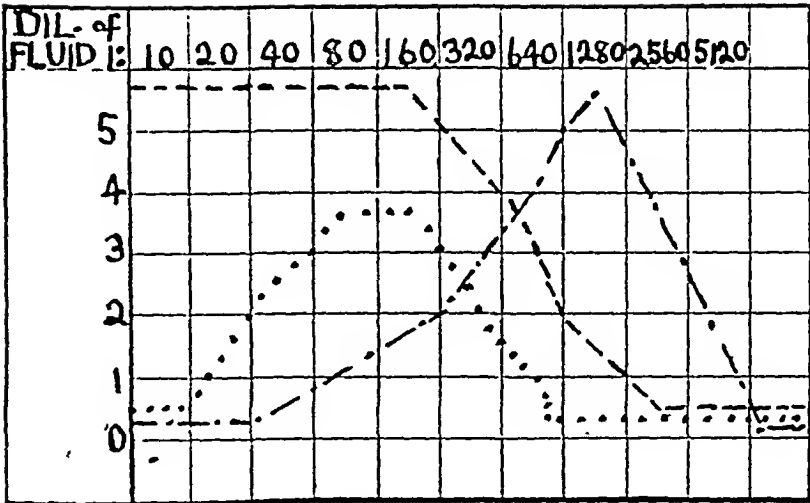


CHART 2.—Curves of cases of paretic, meningitic and syphilitic spinal fluids, reported in Bulletin Johns Hopkins Hospital, 1915, 26, 298. Dilution of fluids in each instance as shown in figures at the top of the chart, 1:10, etc. Paretic, 5555531000; syphilitic, 0123321000; meningitic, 00011245210.

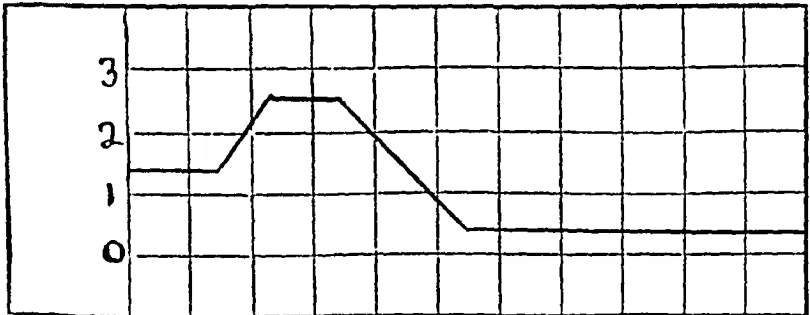


CHART 3.—Curve in forty of our poliomyelitic fluids: 1122100000.

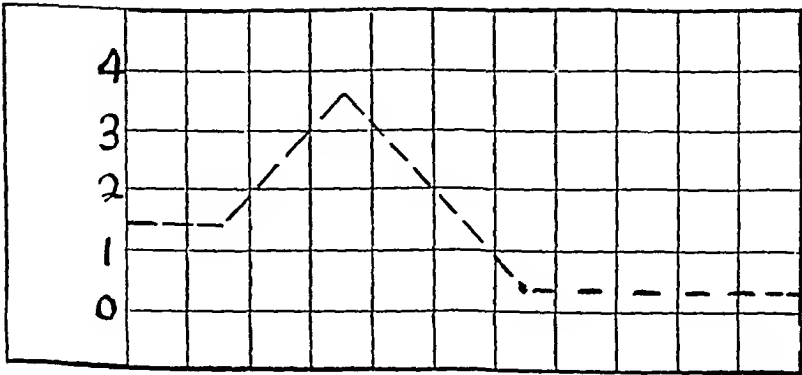


CHART 4.—Curve in eight of our poliomyelitic fluids: 1123210000.

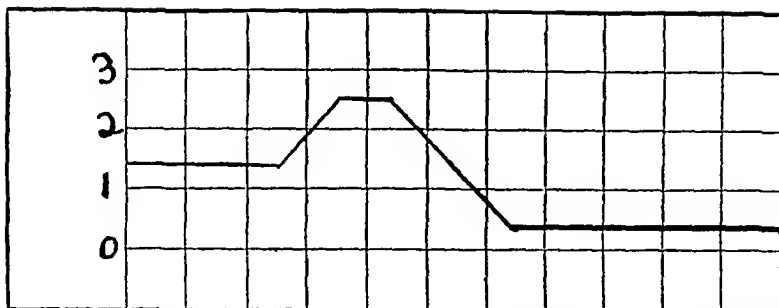


CHART 5.—Curve in six of our poliomyelitic fluids: 111221000.

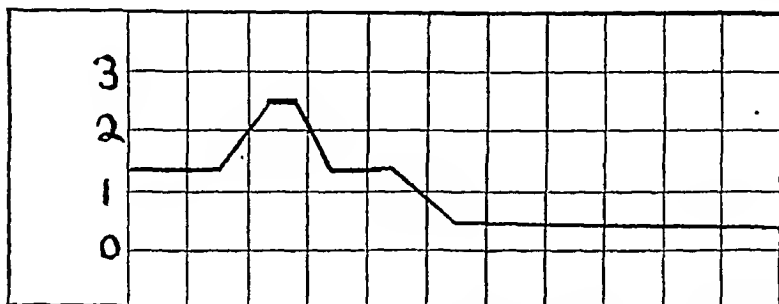


CHART 6.—Curve in five of our poliomyelitic fluids: 112110000.

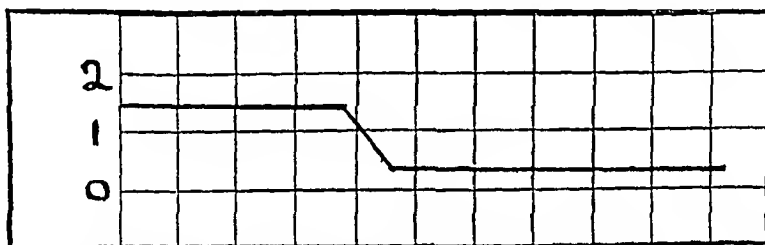


CHART 7.—Curve in fourteen of our poliomyelitic fluids: 111100000.

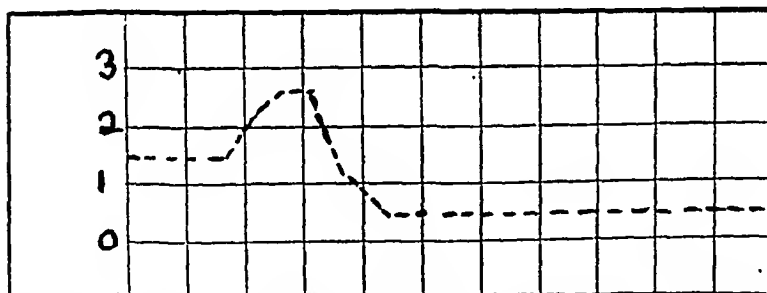


CHART 8.—Curve in four of our poliomyelitic fluids: 1121000000.

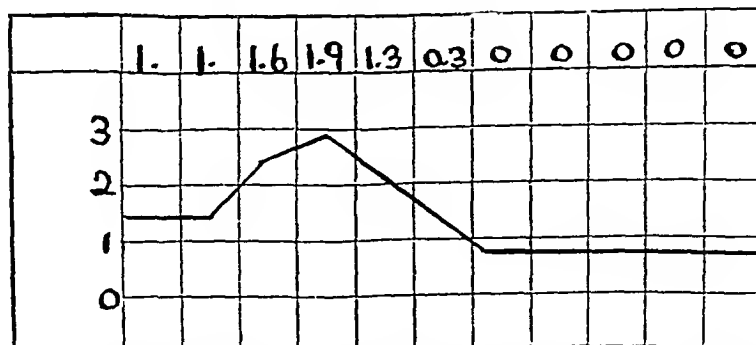


CHART 9.—Composite curve in 114 poliomyelitic fluids: 1122100000.

Every poliomyelitis fluid examined gave a curve falling in one of these six groups, or approximately so, but this cannot be taken to be of absolute diagnostic value, since a few fluids from patients with epidemic and tuberculous meningitis also fell in these groups. Of perhaps greater value is the differentiation of a poliomyelitic fluid, with a practically normal chemistry, and that of meningism. In only one instance was the fluid from a patient with poliomyelitis negative, even with a practically normal chemistry, while the curves from patients with meningism have been negative even with a slightly increased chemistry. Not enough fluids from patients with meningism have been as yet examined to enable us to feel sure that the fluids from them are always negative. If this proves to be true, the gold chlorid curve will be of great value in differentiating poliomyelitis fluid, with slight chemical changes from fluids of meningism.

TABLE 10.—ONE HUNDRED AND FOURTEEN POLIOMYELITIS FLUIDS EXAMINED BY GOLD CHLORID METHOD

Seventy-seven of them fell in one of 6 curves as follows:

	No. of Cases
1122100000.....	40
1123210000.....	8
1112210000.....	6
1121100000.....	5
1111000000.....	14
1121000000.....	4

The other thirty-seven had various curves similar to the foregoing six, and are as follows:

No. of Cases	No. of Cases	No. of Cases
1100000000..... 1	1221100000..... 2	22332100..... 1
1111100000..... 1	1222100000..... 2	22343210..... 1
1111110000..... 2	1223210000..... 3	
1111111100..... 1	1222332100..... 1	2
1111231100..... 1	1232100000..... 2	
1112100000..... 4	1233100000..... 1	
1112110000..... 2	1233210000..... 1	
1112221000..... 1		
1112233210..... 1	12	
1112321000..... 2		
1122110000..... 3		
1122210000..... 2		
1123321000..... 1		
1124432100..... 1		
23		
12		
2		
37		

Normal or meningism curve..... 0000000000 or 1110000000
 Curve of 114 poliomyelitis fluids.... 1122100000
 Curve of 13 tuberculous fluids..... 1112221000
 Curve of 15 epidemic cerebrospinal meningitis 1111233210

2. QUANTITATIVE STUDIES IN SPINAL FLUIDS

JOSEPHINE B. NEAL, M.D., AND R. L. KAHN, Sc.D.

Qualitative studies of the albumin, globulin and glucose, with rough quantitative estimations, have always been made by the meningitis division as a part of the routine examination of spinal fluids. The need of accurate quantitative determinations, however, has been keenly felt.

In view of the more extensive use now made of spinal fluid examinations for diagnosis, it would seem desirable to obtain as comprehensive a knowledge of the subject as possible. Moreover, there is always the hope and the possibility in studying such a new field, that some facts of practical value in the way of diagnosis and prognosis may be brought to light. It was, therefore, a source of great gratification to us when, in connection with the work of the epidemic of poliomyelitis in the summer of 1916, the opportunity was offered us to undertake such studies.

The determinations attempted embrace total, nonprotein, urea and ammonia nitrogen, uric acid, creatin, creatinin, sugar and cholesterol. The methods employed were the adaptations and, in some cases, modifications of the microchemical procedures used in blood investigations. These methods are described somewhat in detail at the end of the article.

With the exception of urea, which has been extensively studied by French workers, quantitative studies in spinal fluids are comparatively few, due, undoubtedly, to the fact that until recently, microchemical methods not being available, most single chemical tests required a larger amount of spinal fluid than was usually obtained at one puncture. Along all the lines of quantitative work the French have contributed most to the subject.

The work up to 1909 is reviewed by Anglada.¹⁵ He gives various tables from different workers and concludes that the normal content of albumin in the spinal fluid is about 15 mg. per 100 c.c., and that normally, this albumin is serum-globulin, while in a true meningitis serum, albumin is also present and the total quantity is greatly increased, running as high as 300 mg. per 100 c.c. The normal urea is given as from 15 to 35 mg. per 100 c.c., and results as high as 438 mg. per 100 c.c. in uremia. The normal sugar is given as 0.045 to 0.055 per cent. He considers 0.06 to 0.10 per cent. or more, as an increase in the glucose, and cites such findings in diabetes and certain toxic and infectious conditions and diseases of the nervous system.

15. Anglada: *Le liquide céphalorachidien*, Paris, 1909.

In cases of meningitis and certain other conditions of the central nervous system, he finds a decrease in the sugar.

In a very complete and extensive study of spinal fluid, Mestrezat¹⁶ gives in normal fluids, the following findings:

Albumin averages18 mg. per 100 c.c.; limit, 13 to 30 mg.

Urea averages 6 mg. per 100 c.c.; limit, 3 to 10 mg.

Sugar averages.....0.053% per 100 c.c.; limit, 0.048 to 0.058%

In purulent meningitis the albumin is increased to 300 and even to 1,160 mg. per 100 c.c.; in tuberculous meningitis, from 100 to 300 mg. per 100 c.c.

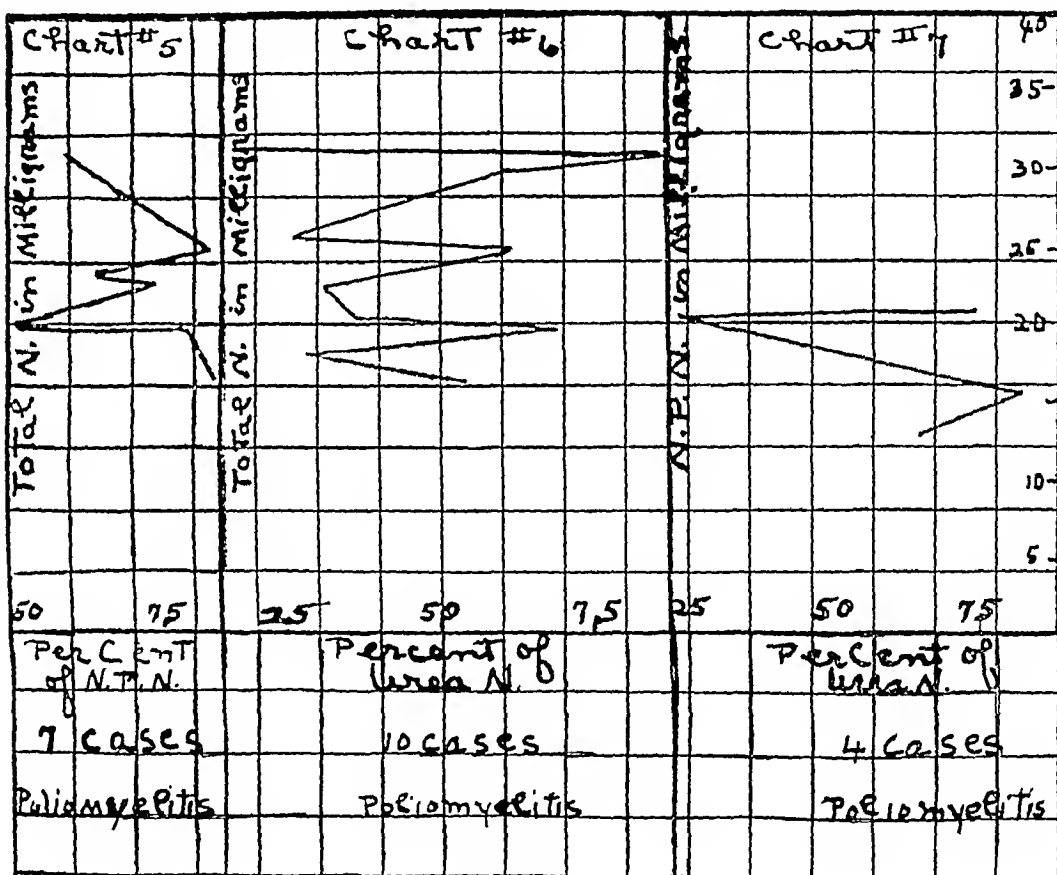


CHART 10

Soper and Granat¹⁷ studied the urea in ninety-seven spinal fluids, having in mind, especially, the relation of the urea content to the prognosis in cases of uremia. The blood urea, also, was examined in certain cases and agreed closely with the content of the spinal fluid, as had been previously stated by other workers. They found the urea varying from 10 to about 50 mg. per 100 c.c. in conditions without nephritis, though in certain cases of tuberculous meningitis it rose to 170 mg. per 100 c.c. They give a very good review of the literature, the earlier work having been done mainly by French workers.

16. Mestrezat: Le liquide céphalorachidien normal et pathologique, Paris, 1912.

17. Soper and Granat: THE ARCHIVES INT. MED., 1914, 13, 131.

According to Plaut, Rehm and Schottmuller,¹⁸ normal spinal fluid contains from 30 to 60 mg. of protein per 100 c.c. These figures are increased in various diseases.

Pfeiffer, Kober and Field¹⁹ studied a number of spinal fluids, mostly from syphilitic cases, with especial reference to the relation of the total protein, total globulin and euglobulin to the Wassermann reaction. They found the amount of protein varying from 20 to 100 mg. per 100 c.c. of fluid. Their fluids were nearly all pathologic.

Rosenbloom,²⁰ studying eleven fluids, found the nitrogen in spinal fluids varying from 0.172 parts per 100 in a normal fluid, to 0.362 in a case of meningitis.

Woods²¹ found, in agreement with earlier workers, that the urea in the blood and spinal fluid was the same. He also observed that the total nonprotein nitrogen was about 25 per cent. lower than in the blood; that is, about 10 mg. per 100 c.c. of fluid. The urea was about 78 per cent. of the total nonprotein nitrogen; the total nonprotein nitrogen in cases of chronic nephritis varied from 17.85 to 188.69 mg. per 100 c.c., and the urea from 11.09 to 166.66 mg. per 100 c.c.

A similar relation between the nonprotein nitrogen in the spinal fluid and blood was reported earlier by Mollard and Froment.²²

The concentration of urea in the spinal fluid, however, appears to be about equal to that in the blood, as is reported by Soper and Granat,¹⁷ Cullen and Ellis²³ and other workers, referred to in the foregoing articles.

Fine and Myers²⁴ found that in nephritis the concentration of creatinin in the spinal fluid is 46 per cent., of creatin 22 per cent., of uric acid 5 per cent. of the concentrations of the respective substances in the blood.

Hopkins²⁵ studied the sugar content of the spinal fluid, comparing it in certain cases with the blood sugar, which he found to be, in normal conditions, about 10 mg. per 100 c.c. higher than in the spinal fluid. He determined the sugar content in 141 cases, including many conditions—meningitis, diabetes, infections, intoxications, epilepsy, nephritis, nervous diseases and syphilis. The earlier work along this line is reviewed.

18. Plaut, Rehm and Schottmuller: *Leitfaden zur Untersuchung der zerebro-spinal Flüssigkeit*, Jena, 1913, p. 16.

19. Pfeiffer, Kober and Field: *Proc. Soc. Exper. Biol. and Med.*, 1915, **12**, 153.

20. Rosenbloom: *Biochem. Bull.*, 1916, **5**, 17.

21. Woods: *THE ARCHIVES INT. MED.*, 1915, **16**, 577.

22. Mollard and Fromet: *Jour. de physiol. et de path. gén.*, 1909, **11**, 263.

23. Cullen and Ellis: *Jour. Biol. Chem.*, 1915, **20**, 511.

24. Fine and Myers: *Proc. Soc. Exper. Biol. and Med.*, 1916, **13**, 70.

25. Hopkins: *Am. Jour. Med. Sc.*, 1915, **150**, 847.

Schloss and Schroeder²⁶ determined the sugar content of a large number of spinal fluids, both normal and pathologic, from infants and children. They concluded that the normal amount varies from 0.05 to 0.134 per cent. In tuberculous meningitis it varied from an amount too small to be determined to normal. In poliomyelitis it was normal in three cases and decreased in a fourth. In epidemic meningitis it was generally decreased at the height of the disease and increased with recovery, a fact previously noted by Connall²⁷ and by DuBois and Neal.²⁸ Kraus and Corneille²⁹ studied the sugar content in the spinal fluid in both normal and pathologic conditions. They found the range for normal fluids to be between 0.045 and 0.110 per cent. They also found a rise in the sugar content in recovering cases of epidemic cerebrospinal meningitis and a decrease in fatal cases.

The presence of cholesterol in spinal fluids has been reported by various workers³⁰ in different forms of paralysis.

In this laboratory the total nitrogen in poliomyelitis was found to be in the neighborhood of 25 mg. per 100 c.c. of spinal fluid. In various forms of meningitis, the total nitrogen was found to be considerably increased, extending from 35 mg. to about 150 mg. per 100 c.c. Total nitrogen determinations alone, however, are of comparatively little value in view of the variations of the nonprotein nitrogen content. This is perhaps well to emphasize, in view of the attempt of Landau and Halpern³¹ to show that a certain antagonism exists between the total nitrogen and chlorids in spinal fluids; that a high finding of the one corresponds to a low finding of the other. A high total nitrogen may often be due to an increase in the nonprotein nitrogen, particularly in the presence of kidney disturbances.

The nonprotein nitrogen content in normal spinal fluid is about 50 to 70 per cent. of the total nitrogen, and urea about 60 to 80 per cent. of the nonprotein nitrogen. In pathologic conditions these relations do not hold.

The determinations of ammonia nitrogen were unsatisfactory, because sufficiently large quantities of a single fluid required for a test were not available. Mixed fluids, therefore, had to be resorted to. This procedure seemed justifiable in view of the fact that Frenkel-Heiden³² was unable to demonstrate ammonia in spinal fluids. The findings show wide variation, with figures ranging from 0.1 mg. to

26. Schloss and Schroeder: *Am. Jour. Dis. Child.*, 1916, **11**, 1.

27. Connall: *Quart. Jour. Med.*, 1909-1910, No. 3, p. 152.

28. DuBois and Neal: *Am. Jour. Dis. Child.*, 1915, **9**, 1.

29. Kraus and Corneille: *Jour. Lab. and Clin. Med.*, 1916, **1**, No. 9.

30. Pighina: *Ztschr. f. Phys. Chem.*, 1909, **61**, 508.

31. Landau and Halpern: *Biochem. Ztschr.*, 1908, **9**, 72.

32. Frenkel-Heiden: *Biochem. Ztschr.*, 1906, 1907, **2**, 188.

0.9 mg. of ammonia nitrogen per 100 c.c. of spinal fluid in poliomyelitis. It might be said, also, that these fluids, although sterile at the time of the determinations, had been kept in the ice-box for several weeks, which might slightly affect the results.

The determinations of uric acid also were carried out on mixed fluids. The results indicate that there are present from 0.25 mg. to 0.50 mg. of uric acid per 100 c.c. of fluid in poliomyelitis.

The quantity of creatinin in poliomyelitis fluid was found to be about 0.5 mg. per 100 c.c., and somewhat less than this amount of creatin. The recent conclusions of Gettler and Baker³³ that normal blood contains no more than 0.5 mg. per 100 c.c. of creatinin is of interest in this connection. If the method of Folin and Denis be correct, then, like urea, creatinin is equally distributed in the blood and spinal fluid.

The finding of sugar in poliomyelitis fluids are about normal, 0.06 per cent. In meningitis the findings are usually lower.

An attempt was made to determine cholesterol in spinal fluids by the method recently suggested by Bloor.³⁴ In no case, however, were the amounts sufficient for quantitative determinations. All fluids tested showed the presence of traces only.

The results in detail are given in the accompanying tables.³⁵

METHODS

Total Nitrogen.—The method employed for the determination of total nitrogen in spinal fluids was a modification of the direct nesslerization method recently developed by Folin and Denis.³⁶ The modification in detail is presented in another place.³⁷ In this connection, only a brief outline of the procedure will be given.

Procedure: Two c.c. of spinal fluid are pipetted into a test tube, 1 c.c. of the concentrated acid mixture (containing 1 volume concentrated sulphuric acid, 3 volumes concentrated phosphoric acid and $\frac{1}{15}$ volume of a 10 per cent. solution of copper sulphate) added and the digestion carried out over a microburner until the appearance of white sulphuric acid fumes. The mouth of the test tube is then covered with a watch glass and heating continued for about a minute. The color obtained is usually straw yellow. After permitting the test tube to cool, the contents are rinsed quantitatively into a 100 c.c. volumetric flask, using about 60 c.c. of water in the process. A quantity of 10 per cent. sodium hydroxid is then added sufficient to neutralize the concentrated acid and permit a surplus of 2 c.c. of alkali, and filtered. Into another 100 c.c. volumetric flask are pipetted 1 c.c. of the concentrated acid mixture, diluted, 20 c.c. of the standard ammonium sulphate solution containing 1 mg. ammonia nitrogen and an amount of 10 per cent. alkali solution equal to that added to the unknown. This is also made up to volume, shaken and filtered.

33. Gettler and Baker: Jour. Biol. Chem., 1916, **25**, 211.

34. Bloor: Jour. Biol. Chem., 1916, **24**, 227.

35. Dr. Kahn was assisted by Mr. Benjamin Shapiro in the technical work.

36. Folin and Denis: Jour. Biol. Chem., 1916, **26**, 473.

37. Kahn: Jour. Biol. Chem., 1916, **28**, 203.

Aliquot portions of these filtrates are employed for nesslerization. Thus, 50 c.c. of the water-clear filtrates of both the unknown and standard are pipetted into two 100 c.c. volumetric flasks, diluted to about 75 c.c. with water, and 10 c.c. of Nessler's solution added to each, made up to volume, shaken and the colors compared on the colorimeter. The same results could be obtained by using 50 c.c. volumetric flasks and employing 25 c.c. quantities of respective filtrates for nesslerization.

Nonprotein Nitrogen.—Procedure: To 5 c.c. of spinal fluid in a large test tube are added, quantitatively, 2 c.c. of a freshly prepared 25 per cent. solution of glacial phosphoric acid. The test tube is then stoppered, shaken and permitted to stand one to twenty-four hours and filtered through a small dry filter paper. Either 5 or 3 c.c. quantities of the water-clear filtrates are used for a nitrogen determination, the procedure being identical with that described for total nitrogen.

Urea Nitrogen.—Procedure: To 5 c.c. of spinal fluid in a 100 c.c. volumetric flask are added about 5 c.c. of water and 0.1 gm. of dry urease, shaken and permitted to stand at room temperature from twenty to forty minutes. This is then diluted with about 50 c.c. of water, 2 c.c. of freshly prepared glacial phosphoric acid added, also 0.5 gm. of Merck's charcoal, and made up to volume. This is shaken from time to time and allowed to stand for forty-five minutes or more, when it is ready to be filtered. Definite portions of the water-clear filtrates are used for nesslerization, as in the cases of the total and nonprotein nitrogen determinations.

Ammonia Nitrogen.—Procedure: To 25 c.c. spinal fluid are added 3 c.c. of glacial phosphoric acid, mixed, allowed to stand about an hour and filtered; 25 c.c. of the filtrate are pipetted into a 50 c.c. volumetric flask, 5 c.c. Nessler's solution added, made up to volume and compared with a standard ammonium sulphate solution containing 0.25 mg. nitrogen in 100 c.c.

Uric Acid.—Procedure: The Benedict³⁸ modification of the Folin and Denis³⁹ method was employed. Twenty-five c.c. spinal fluid are added to boiling hundredth normal acetic acid in a casserole, boiling continued for about a minute, removed from the flame, about 200 c.c. of boiling water added and poured over a folded filter. The filtrate is then concentrated to about 50 c.c., cooled, and about 0.5 c.c. of dialyzed iron added drop by drop, shaking with each addition, then filtered and the water-clear filtrate concentrated to about 2 to 3 c.c.; transferred quantitatively to a centrifuge tube, using about 5 c.c. of hot water to wash out the vessel. To the solution in the centrifuge tube is now added about 15 drops of ammonia-silver-magnesia mixture, allowed to stand for about ten minutes to permit precipitation, when it is centrifuged at a high speed for about five minutes. The supernatant fluid is poured off and excess of ammonia drawn off by inverting the tube on filter paper; 2 drops of a 5 per cent. solution of KCN are added to dissolve the precipitate, also 1 c.c. of the phosphotungstic acid reagent and about 8 c.c. of saturated solution of sodium carbonate. This is permitted to stand for a minute, transferred into a 25 c.c. or 50 c.c. volumetric flask, depending on the intensity of the color, made up to volume with water and compared with the standard on the Duboscq' colorimeter. The latter is prepared by pipetting 5 c.c. of the uric acid standard solution into a 50 c.c. flask, and adding 2 drops of the KCN solution, 2 c.c. of phosphotungstic acid reagent and 15 c.c. of saturated sodium carbonate, and making up to the mark with water.

Creatinin and Creatin.—Procedure: For the determinations of creatinin and creatin the Folin and Denis⁴⁰ methods were employed. These methods have recently been criticized by McCrudden and Sargent.⁴¹ The results, never-

38. Benedict: Jour. Biol. Chem., 1915, **20**, 629.

39. Folin and Denis: Jour. Biol. Chem., 1912-1913, **13**, 469.

40. Folin and Denis: Jour. Biol. Chem., 1914, **17**, 475.

41. McCrudden and Sargent: Jour. Biol. Chem., 1916, **26**, 527.

theless, seem worth repeating in view of the creatinin and creatin studies on blood by the same methods. To 5 c.c. of spinal fluid are added 20 c.c. of saturated solution of picric acid, filtered, and 10 c.c. quantities of the filtrate employed for creatinin and creatin determinations, respectively. The standards employed are solutions of creatinin in saturated picric acid. The color is developed by adding 0.5 c.c. of 10 per cent. sodium hydroxid solution and allowing to stand ten minutes. Several standards are prepared and the color of the unknown matched with the one which approached it closest in intensity. In the case of the creatin determinations, the standard also was autoclaved. This, it is believed, reduced the chances of error considerably.

Sugar.—This was determined by means of the Lewis and Benedict⁴² method slightly modified.

Procedure: Four volumes of saturated solution of picric acid are added to 1 volume of spinal fluid, shaken and filtered. To 3 c.c. of the filtrate in a test tube graduated to the 10 c.c. mark is added 1 c.c. of saturated solution of sodium carbonate and placed in boiling water for about twenty minutes, after which it is cooled and made up to 10 c.c. with water. The standard employed is a solution of glucose (Kahlbaum) in saturated picric acid. To 3 c.c. of this solution containing 0.5 mg. of glucose is added 1 c.c. of saturated sodium carbonate solution, kept in a waterbath for about twenty minutes, cooled, made up to 10 c.c. and compared on the colorimeter with the unknown.

Seventy-five poliomyelitis fluids were tested for six substances—total nitrogen, nonprotein nitrogen, urea nitrogen, creatinin, creatin and sugar (Table 11). They showed the variations set forth in Table 12. The outcome of these seventy-five cases varied from complete recovery to death. The percentages of the substances named found in each fluid gave no indication of the final outcome.

Table 13 shows the results of the examination of spinal fluids in cases of purulent meningococcic, streptococcic and influenzal meningitis. Table 14 shows the results of successive punctures in the cases of epidemic cerebrospinal meningitis (E. C. S. M.) of Table 13. Twenty-three successive fluids from eight cases of epidemic cerebrospinal meningitis were tested for the six substances, total nitrogen, nonprotein nitrogen, urea nitrogen, creatinin, creatin and sugar. They showed the variations set forth in Table 15.

Table 16 shows the results of the examination of the spinal fluid in seventeen cases of tuberculous meningitis. Table 17 shows the variations in the findings of the substances examined for.

Table 18 gives the results of the examination of a number of fluids in various affections, and Table 19 shows the variation in total nitrogen, nonprotein nitrogen, urea nitrogen and sugar in six normal spinal fluids which were tested.

Table 20 gives the median of the total nitrogen, nonprotein nitrogen, urea nitrogen, creatin, creatinin and sugar in the various diseases. The median is used instead of the average, as it is the truer index of the greater incidence of values. It is obvious in estimating averages that a few very high or very low determinations will unduly influence the result.

42. Lewis and Benedict: Jour. Biol. Chem., 1915. 20, 61.

TABLE 11.—RESULTS OF SPINAL FLUID EXAMINATIONS IN POLIOMYELITIS

No.	Case	Quantitative Determinations						Qualitative Determinations*			Outcome
		Total N	Non-protein N	Urea N	Creatinln	Creatln	Sugar	Albumin	Globulin/	Fehling's	
2482a†	Polio.	0.515	0.405	0.084	±,	±,	+++	Recovered
2516a	Polio.	0.500	0.449	0.082	++,	+++,	+++	Both legs paralyzed
2535a	Polio.	0.492	0.445	0.098	+	+	+++	O. K.
2517a	Polio.	0.465	0.417	0.080	+	+	+++	8 weeks; slight weakness of arms and hands
2518a	Polio.	0.454	0.495	0.092	+	+	+++	Recovered
2682a	Polio.	0.088	+	+	+++	
2662a	Polio.	0.059	+	+	+++	
2542a	Polio.	0.053	++,	++,	+++	Recovered
2618a	Polio.	0.072	++.	+1,	+++	Recovered
2685a	Polio.	0.100	+++1,	+++1,	+++	Died
2792a	Polio.	0.061	+	+	+++	No paralysis
2841a	Polio.	0.087	+	+sl.,	+++	Recovered
2834a	Polio.	0.055	+1,	++,	+++	4 weeks; weak back; paralysis of lower extremities
2895a	Polio.	0.025	+1,	+1,	+++	12 weeks; weakness of leg
2916a	Polio.	0.463	0.190	0.0602	+	+	+++	Recovered
3096a	Polio.	0.273	Traces	+sl.,	+	++	O. K.
3101a	Polio.	0.0742	+sl.	+	+++	O. K.
3092a	Polio.	0.560	0.0742	+sl.,	+1,	+++	Died
3094a	Polio.	0.360	0.0523	+	+	+++	
3196a	Polio.	0.388	0.319	0.0753	+sl.,	+sl.,	+++	Left deltoid; left facial paralysis
3197a	Polio.	0.400	0.314	0.0781	++,	++,	+++	Died
3236b	Polio.	0.387	0.448	0.0512	+	+1,	+++	Weak left lower; brace
3241a	Polio.	25.00	20.95	15.68	0.400	0.314	0.0508	+	+	+++	8 weeks; double pelvic brace
3242b	Polio.	22.87	6.93	0.350	0.350	0.060	+	+	+++	Weak right arm
3245b	Polio.	0.326	0.054	+++,	+++,	+++	Paralysis lower extremity
2994b	Polio.	0.609	0.0613	+	++,	+++	Died
2989b	Polio.	0.378	Traces	+1,	+1,	++	Died
3007a	Polio.	0.403	+	+	+++	Recovered
2998b	Polio.	0.323	0.0595	+	+	+++	Died
2979a	Polio.	0.454	0.0454	+sl.,	+	+++	
3139a	Polio.	0.1063	+	+	+++	Died
3140a	Polio.	0.0552	+	+	+++	Died
3109a	Polio.	0.0588	+	+	+++	
3274b	Polio.	0.396	0.0810	+	+	+++	No definite paralysis
3196b	Polio.	0.429	0.0824	+	+	+++	Left deltoid; left facial paralysis
3274a	Polio.	0.0641	+	+	+++	No definite paralysis
3207a	Polio.	15.25	++,	++,	+++	Weak right deltoid
3252a	Polio.	17.33	+	+	+++	O. K.

* The + marks in this column in all tables indicate the albumin, globulin and reduction of Fehling's solution, respectively.

† Successive fluids from the same cases are indicated by a, b, c, etc.

TABLE 11.—RESULTS OF SPINAL FLUID EXAMINATIONS IN POLIOMYELITIS—(Continued)

No.	Case	Quantitative Determinations						Qualitative Determinations			Outcome
		Total N	Non-protein N	Urea N	Creat-inin	Crea-tin	Sugar	Albu-min	Globu-lin/	Feh-ling's	
3310b	Polio.	22.72	14.56	+	+	+++	8 weeks; left fac- ial weakness
3314b	Polio.	33.30	++	++	+++	Unable to sit up; left post. splint
3315c	Polio.	25.85	6.62	+	+	+++	8 wks.; weak low- ers; slight weak- ness of uppers
3300a	Polio.	21.00	11.0(?)	+	+	+++	8-weeks; relaxed abdominal mus- cles
3307b	Polio.	24.25	12.50	++	+1	+++	Recovered
3322b	Polio.	12.50	++1	++1	+++	8 weeks; left fac- ial paralysis
3327c	Polio.	13.72	++++	++++	++	O. K.
3324b	Polio.	16.34	++++	++++	+++	Left deltoid weakness
3331a	Polio.	34.00	20.66	5.35	++	+	+++	Died
3341b	Polio.	30.00	18.51	++	++	+++	O. K.
3342b	Polio.	12.13	+	+	+++	No definite par- alysis
3343b	Polio.	12.03	+sl.	+	++++	No paralysis noted
3354a	Polio.	11.36	++++	++++	+++	No definite par- alysis; weak gluteals
3357b	Polio.	22.57	16.64	++	+1	+++	
3359c	Polio.	26.25	+1	+1	++++	Weak right glu- teals and right lumbar muscles
3196d	Polio.	19.50	15.54	13.12	+1	++	+++	Left deltoid; left facial paralysis
3358d	Polio.	14.01	++	+1	+++	8 wks.; posterior splints
3361c	Polio.	17.87	++	++1	+++	Died
3310c	Polio.	9.61	+1	++	+++	8 wks.; weak left quadriceps ex- tensor
3376c	Polio.	18.42	+	+sl.	+++	O. K.
3300b	Polio.	20.61	7.81	+1	+1	+++	Relaxed abdom- inal muscles
3322c	Polio.	17.85	++	++	+++	Paralysis of left facial; 8 weeks
3379b	Polio.	16.87	+	+	+++	8 wks.; slight fac- ial paralysis; slight weakness of both quadri- ceps extensors
3384a	Polio.	20.00	++	++	+++	Died
3324c	Polio.	20.68	++	++1	+++	
3274c	Polio.	21.42	++	++	+++	No definite par- alysis
3397a	Polio.	16.37	13.72	8.83	+	+sl.	+++	8 weeks; weak thigh and back muscles
3392a	Pollo.	17.48	5.06	+1	+1	+++	Right arm and leg paralysis
3410c	Pollo.	20.75	+	+1	+++	Paralysis left quadriceps ex- tensor
3341c	Polio.	15.88	+1	+1	+++	O. K.
3412c	Polio.	22.62	++	+++	+++	Right deltoid
3436a	Polio.	24.62	14.62	++	++1	+++	Died
3439a	Pollo.	24.78	++	++1	+++	Died
3497a	Pollo.	31.25	26.6	+	+	+++	
2842a	Pollo.	(?)	0.0523	+1	++	+++	
3523a	Pollo.	16.87	8.91	0.528	0.0943	+1	+1	+++	

TABLE 12.—FINDINGS IN SUCCESSIVE PUNCTURES

	Number of Fluids	Variation per 100 C.c., Mg.
Total nitrogen.....	24	16.37 to 34.00
Nonprotein nitrogen.....	16	8.91 to 24.78
Urea nitrogen.....	17	5.06 to 26.6
Creatinin.....	22	0.273 to 0.609
Creatin.....	11	0.190 to 0.495
Sugar.....	36	0.025 to 0.1063

TABLE 13.—RESULTS OF EXAMINATION OF SPINAL FLUIDS IN
PURULENT MENINGITIS

No.	Case	Quantitative Determinations						Qualitative Determinations			Outcome
		Total N	Non- protein N	Urea N	Creat- inin	Creat- tin	Sugar	Albu- min	Globu- lin	Feh- ling's	
3017a	Epidemic cerebrospinal meningitis	0.595	Traces	++++, +++++, ++			O. K.
3225a	Epidemic cerebrospinal meningitis	0.326	Traces	+++ , +++ , —			O. K.
3222c	Epidemic cerebrospinal meningitis	45.15	14.12	+++ , +++ , +++			O. K.
3268a	Epidemic cerebrospinal meningitis	34.25	15.86	++ , ++ , +1			O. K.
3302b	Epidemic cerebrospinal meningitis	62.20	10.25	++++, +++++, +			Died
3363a	Epidemic cerebrospinal meningitis	24.46	++++, +++++, ++			O. K.
3386a	Epidemic cerebrospinal meningitis	39.80	+++ , ++++ , ±			Died
3442a	Influenzal meningitis	40.25	6.28	++++, +++++, —			Died
3468c	Influenzal meningitis	138.75	++++, +++++, —			Died
3472a	Influenzal meningitis	51.50	++++, +++++, ±			Died
3500a	Streptococcus meningitis	86.30	11.10	++++, +++++, —			Died
3541a	Epidemic cerebrospinal meningitis	60.50	46.66	15.15	67.1*	21.7†	Traces	++++, +++++, —			
3574a	Epidemic cerebrospinal meningitis	Traces	+++ , +++ , —			O. K.
3545b	Streptococcus meningitis	23.35	18.08	77.4*	0.075	++++, +++++, —			

* Per cent. of nonprotein nitrogen in total.

† Per cent. of urea in total.

TABLE 14.—RESULTS OF SUCCESSIVE PUNCTURES IN CASES OF
EPIDEMIC CEREBROSPINAL MENINGITIS

No.	Quantitative Determinations						Qualitative Determinations			Outcome
	Total N	Non-protein N	Urea N	Per Cent. of N. P. N. in Total	Per Cent. Urea in Total	Sugar	Albu- min	Globu- lin	Feh- ling's	
3441										
2d puncture	120.0	33.47	21.62	++++, +++++, +			O. K.
5th puncture	36.75	+++ , +++ , ++			
3473										
1st puncture	50.00	++++, +++++, —			O. K.
2d puncture	53.75	++++, +++++, +			
4th puncture	47.15	26.62	9.20	++++, +++++, +			
5th puncture	43.45	21.93	11.60	++++, +++++, +++			
3487										
1st puncture	95.00	45.83	36.48	++++, +++++, —			Died
2d puncture	250.00	136.25	53.28	++++, +++++, —			
3044										
4th puncture	73.50	26.60	0.535*	0.704†	Traces	++++, +++++, ±			Died
5th puncture	0.476*	Traces	++++, +++++, ±			
6th puncture	0.476*	0.0628	++++, +++++, ±			
3512										
1st puncture	53.50	25.47		47.6		Traces	++++, +++++, —			Died
4th puncture	29.37	13.62	46.3	Traces	++++, +++++, —			
5th puncture	43.25	15.00	34.6	++++, +++++, —			
6th puncture	47.35	19.55	6.14	41.2	12.9	++++, +++++, —			
7th puncture	40.53	18.25	7.72	45.0	19.0	Traces	++++, +++++, —			
8th puncture	48.50	19.55	7.54	40.3	15.5	Traces	++++, +++++, —			
9th puncture	128.00	31.36	9.25	24.5	7.2	Traces	++++, +++++, —			
3530										
1st puncture	52.00	21.85	10.41	42.0	20.0	Traces	++++, +++++, —			O. K.
2d puncture	++++, +++++, —			
3525										
1st puncture	36.10	20.58	10.25	57.0	28.3	Traces	++++, +++++, —			O. K.
2d puncture	39.25	22.94	6.38	58.4	16.2	Traces	++++, +++++, —			
3d puncture	46.25	21.77	9.25	47.0	20.0	Traces	++++, +++++, —			
4th puncture	6.87	Traces	++++, +++++, —			
5th puncture	71.00	25.69	9.61	36.1	13.5	Traces	++++, +++++, —			
6th puncture	45.45	20.63	5.43	45.3	11.7	Traces	++++, +++++, —			
7th puncture	86.00	27.36	9.85	31.8	11.4	Traces	++++, +++++, —			
8th puncture	6.43	Traces	++++, +++++, —			
13th puncture	9.47	++++, +++++, +++			
3551										
1st puncture	22.72	13.00	5.11	57.2	22.4	Traces	++++, +++++, —			O. K.
3d puncture	3.66	Traces	+++ , ++ , ++			
4th puncture	6.77	+++ , +++ , +			
5th puncture	4.55	+++ , +++ , +++			

* Creatinin.

† Creatin.

TABLE 15.—RESULTS OF TESTS OF TWENTY-THREE SUCCESSIVE FLUIDS FROM
EIGHT CASES OF EPIDEMIC CEREBROSPINAL MENINGITIS
SHOWING VARIATIONS

	Number of Fluids	Variations per 100 C.e. Mg.
Total nitrogen.....	9	22.72 to 250.00
Nonprotein nitrogen.....	9	13.00 to 136.25
Urea nitrogen.....	9	3.66 to 53.28
Creatinin.....	9	0.326 to 0.595
Creatin.....	9	0.704 to
Sugar.....	9	Traces to 0.0628
Per cent. nonprotein nitrogen in total....	15	24.5 to 58.4
Per cent. urea nitrogen in total.....	15	7.2 to 28.3

If the termination was favorable, nitrogen, nonprotein nitrogen and urea were decreased; sugar was increased; if the termination was unfavorable, opposite results were obtained.

TABLE 16.—RESULTS OF TESTS OF CEREBROSPINAL FLUIDS IN
TUBERCULOUS MENINGITIS

No.	Case	Quantitative Determinations						Qualitative Determinations			Outcome
		Total N	Non- protein N	Urea N	Creat- inin	Crea- tin	Sugar	Albu- min	Globu- lin	Feh- ling's	
2508b	Tuberculous men- ingitis	0.487	0.563	0.060	++	+++	+++	Died
2401a	Tuberculous men- ingitis	0.765	0.735	0.028	+++	+++	+	
3115a	Tuberculous men- ingitis	Traces	++	++	+sl.	Died
2966a	Tuberculous men- ingitis	Traces	++	++	++	Died
3284a	Tuberculous men- ingitis	34.50	6.66	++	+	++	Died
3333a	Tuberculous men- ingitis	34.40	++++	++++	+	
3339b	Tuberculous men- ingitis	29.70	17.25	7.93	++++	++++	+++	Died
3335a	Tuberculous men- ingitis	42.50	14.18	++++	++++	—	
3434a	Tuberculous men- ingitis	24.35	11.50	++	++	+	Died
3304c	Tuberculous men- ingitis	26.50	13.88	7.06	+++	+++	++	Died
3469a	Tuberculous men- ingitis	25.25	15.44	++++	++++	++	Died
3478b	Tuberculous men- ingitis	20.86	++++	++++	++	Died
3514a	Tuberculous men- ingitis (?)	16.3	9.05	3.13	55.5*	19.2†	++	++	—	
3520a	Tuberculous men- ingitis	23.35	12.82	54.9*	Traces	++++	++++	—	
3547a	Tuberculous men- ingitis	22.72	Traces	++++	++++	—	
3583a	Tuberculous men- ingitis	7.22	++++	++++	+	
3584a	Tuberculous men- ingitis	4.54	++++	++++	+	

* Per cent. of nonprotein nitrogen in total.

† Per cent. of urea in total.

TABLE 17.—SHOWING VARIATIONS IN THE FINDINGS IN SEVENTEEN CASES OF TUBERCULOUS MENINGITIS

	Variations per 100 C.c., Mg.
Total nitrogen.....	20.86 to 34.50
Nonprotein nitrogen.....	12.82 to 17.25
Urea nitrogen.....	4.54 to 14.18
Creatinin.....	0.487 to 0.7652
Creatin.....	0.563 to 0.735
Sugar.....	Traces to 0.060

TABLE 18.—RESULTS OF EXAMINATION OF MISCELLANEOUS FLUIDS

No.	Case	Quantitative Determinations						Qualitative Determinations			Outcome
		Total N	Non-protein N	Urea N	Creatinin	Creatin	Sugar	Alb. min	Globulin	Fehling's	
2821a	Meningism; typhoid	0.066	+	+	+++	Died
3095a	Meningism; endocarditis	0.365	0.0806	+	+	+++1	
3113b	Meningism; intestinal trouble	0.0824	+sl.	+sl.	+++	
3244a	Possible brain tumor	0.350	0.051	+++	+++	+++	O. K.
3138a	Rheumatism	45.25	31.06	14.81	+	+	+++	
?	Syphilis	23.35	19.38	+	+	+++	
3251a	Cerebrospinal lues	0.373	0.377	0.048	+	+sl.	+++	Improved
3240a	Normal (?)	14.35	+	+	+++	
3495a	Normal	15.70	13.69	±	+sl.	+++	
3515a	Meningism	10.18	6.46	63.4†	±	±	+++	O. K.
3516a	Meningism	15.30	13.63	89.4*	0.0888	±	±	+++	
3528a	Syphilis	19.45	14.15	72.7*	0.075	±	±	+++	
3529a	Meningism with pneumonia	9.67	5.35	55.3†	0.0923	±	±	+++	O. K.
3569a	Meningism	12.05	±	±	+++	
3571a	Staph. albus meningitis	Traces	++++, +++++, ±			
3593d	Meningism with pneumonia	22.72	22.38	10.00	98.5*	44.0†	0.0798	+	+	+++	

* Per cent. of nonprotein nitrogen in total.

† Per cent. of urea in total.

TABLE 19.—SHOWING VARIATIONS IN THE FINDINGS IN SIX NORMAL FLUIDS

	Variations per 100 C.c., Mg.
Total nitrogen.....	9.67 to 15.70
Nonprotein nitrogen.....	13.63 to 13.69
Urea nitrogen.....	5.35 to 12.05
Sugar.....	0.0824 to 0.0923

TABLE 20.—MEDIAN CEREBROSPINAL FLUID FINDINGS IN VARIOUS DISEASES

	Total Nitrogen, Mg. per 100 C.c.	Nonprotein Nitrogen, Mg. per 100 C.c.	Urea Nitrogen, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Creatin, Mg. per 100 C.c.	Sugar. Per Cent.
Poliomyelitis.....	22.57 25 cases	15.71 16 cases	12.50 17 cases	0.400 22 cases	0.405 11 cases	0.0613 37 cases
Epidemic cerebrospinal meningitis.....	47.25 30 cases	21.93 23 cases	9.25 26 cases	0.476 5 cases	0.704 1 case	Traces 23 cases
Tuberculous meningitis....	25.88 10 cases	13.88 5 cases	7.14 8 cases	0.626 2 cases	0.649 2 cases	Traces 6 cases
Miscellaneous.....	23.04 14 cases	18.08 7 cases	10.00 7 cases	0.365 5 cases	0.377 1 case	0.075 12 cases

3. ANIMAL INOCULATION EXPERIMENTS

H. L. ABRAMSON, M.D.

POLIOMYELITIS IN MONKEYS FROM VIRUS OF THE 1916 EPIDEMIC

Landsteiner and Popper first produced poliomyelitis in monkeys in 1909. Since then workers in poliomyelitis the world over have performed similar experiments with success. This epoch-making discovery has served as an entering wedge to such workers as Landsteiner, Leviditi, Flexner and Lewis, Roemer and Joseph, Kling, Petterson and Wernstedt, and many others, who have greatly increased our knowledge of the etiologic agent of acute poliomyelitis.

The present work was instituted at the Bureau of Laboratories for the purpose of furnishing fresh material to the entire group of workers for the following studies:

1. Characteristics of the virus of the 1916 epidemic.
2. Isolation and cultivation of organisms said to be the cause of acute poliomyelitis.
3. Immunity problems, active and passive.
4. Problems of transmission.

The first attempts to produce the disease in monkeys resulted in failure. On account of lack of a fresh supply of monkeys, two animals, both of the rhesus variety, that had been the property of the department for several years, were used. These received heavy suspensions of material from the brain and cords of two patients that were clinically and pathologically undoubted cases of acute poliomyelitis. The animals received 0.5 c.c. of a 20 per cent. saline emulsion intracerebrally and 2 c.c. of the same suspension into the tissues around

each sciatic nerve. After one month's observation, these inoculations were repeated with the glycerinated material of the same cases, but in addition they received 10 c.c. of the virus suspension intraperitoneally. These inoculations were no more successful than the first. These monkeys, 98 and 102, later received massive inoculations by three routes, intracerebral, perisciatic and intraperitoneal, of known virulent material from a monkey of the second generation. This, too, proved unsuccessful. It was decided that these monkeys were very refractory and would serve as a source of immune serum for later experiments.

Brain and cord material from three new cases that were clinically positive cases of acute poliomyelitis was then inoculated by three routes, intracerebral, perisciatic and intraperitoneal, into two monkeys from a fresh supply, one being a rhesus and the other a sapajou, a South American ring tail monkey. They received 0.5 c.c., 2 c.c. and 10 c.c. of a 20 per cent. suspension of this material, respectively, in the three ways above mentioned.

On the seventh day after the inoculation, Monkey 1, *Macaccus rhesus*, presented tremor of the head and weakness in the left leg. This condition progressed to complete paralysis of all the limbs, first the left leg, then right leg, left arm, right arm, convulsions and respiratory failure. The monkey died on the third day after the appearance of the muscular weakness. Monkey 2, sapajou, exhibited no symptoms at this writing, three and one-half months after inoculation. Two other animals of this variety were subsequently inoculated with a virulent virus, but these, too, were unsuccessful, confirming the unsuitability of this type of monkey for experimental work in the study of poliomyelitis.

No further difficulty was experienced in passing the virus obtained from Monkey 1 through a series of sixteen monkeys, fourteen of the rhesus variety and two South African mangabeys. The virus is now in the eighth generation and exhibits evidence of increased virulence.

The animals of the second and third generations were inoculated with heavy suspensions of the brain and cord material by the three ways, intracerebral, perisciatic and intraperitoneal, but subsequent animals were infected by injection of 0.5 c.c. of 10 per cent. suspensions into the brain. The last two animals received 0.5 c.c. of 5 per cent. suspension intracerebrally.

TECHNIC

The technic followed was that in use at the laboratory for the preparation of antirabic treatments. Fresh brain and cord material was weighed and ground up in a sterile mortar and sterile salt solution added to make the desired strength. The intracerebral inoculations were made always into the right cerebral hemisphere. The animals were anesthetized. An incision was made in the middle of the scalp over the forward part of the skull. The wound was retracted to the right side and a small trephine opening made with an awl

in the right frontal bone $\frac{1}{4}$ inch anterior to the coronal suture, just to the right of the sagittal suture. The suspension was injected very slowly. It is well not to incise the pericranium, for, if intact, it acts as a valve over the site of the trephine opening and prevents the escape of the injected material. The retracted scalp when it resumes its normal position also aids in the prevention of leakage. In performing the perisciatic inoculations, care was taken to place the needle in close relation to the posterior aspect of the middle of the femur before expelling the material.

Of the seventeen animals inoculated, all but two, *Macacus rhesus* 50 and 51, exhibited frank signs of paralysis. On the fourth day after the inoculation, No. 50 became quite subdued and huddled in a corner of the cage. On being forced to move, it was noticed that he limped slightly on the left hind leg. This animal then received two intraspinal injections of serum obtained from *Macacus rhesus* 102 on successive days. The animal seemed to improve rapidly, and at this date shows no weakness in any limb.

Macacus rhesus 51 exhibited symptoms of distress on the fourth day after inoculation, which consisted of tremors and general weakness; but showed no evidence of paralysis in any limb. This general muscular weakness progressed and the monkey died on the third day after onset of symptoms. The brain showed hyperemia, and sections of the cord presented redness and swelling of the gray matter. The lungs and other organs were apparently normal. This form of the disease in monkeys has been encountered many times by workers in this field and has been called the marantic type of monkey poliomyelitis. Subsequent inoculations with material from this animal produced the typical spinal type of paralysis.

The incubation period in this series was from four to thirteen days. Eight, or 47 per cent., developed paralysis on the seventh day; two on the eighth day; two on the fourth day, and one each on the fifth, tenth, eleventh, twelfth and thirteenth days after the inoculation.

Twelve of the seventeen animals died, a mortality of 71 per cent. Of the remaining five, four exhibit residual paralyses. The average duration of illness for eleven of the twelve fatal cases was four days, the limits being two and seven days. *Macacus rhesus* 25 died twenty days after onset of paralysis. This animal had been inoculated with brain and cord material from a rabbit that had exhibited flaccid paralysis of a progressive type. This inoculation produced no effects, and after an observation period of six weeks, was again inoculated along with two other animals, 36 and 37, with material from No. 26, fourth generation. The incubation period of Nos. 36 and 37 was seven days. That of No. 25 was thirteen days. With the onset of symptoms the paralysis progressed rapidly for three days. Then the process appeared to subside and the animal improved over a period of nearly two weeks. After this quiescent period, the paralysis began where it had left off,

and the animal died of respiratory failure on the twentieth day of the disease.

The character of the paralysis in all but two of the animals was that of the progressive, spinal type, beginning in the left leg, progressing to the right leg, left arm, right arm, and, in the fatal cases, to respiratory paralysis. In one animal, paralysis appeared first in the right leg, then left leg, left arm, right arm, and paralysis of respiration. In the other, the symptom appeared first in the left arm, right arm, then simultaneously in both legs and respiratory paralysis. In the nonfatal cases, except No. 50, the paralysis extended to the left arm, leaving the right arm untouched. With the cessation of the progress of the disease, the left arm recovered its power to some extent, but the paralysis of the legs was permanent.

The gross pathologic changes presented a similar appearance in all the fatal cases, consisting in moderate congestion of the pial vessels of brain and cord. Cut sections of cord at various levels presented a reddening and swelling of the gray matter, rendering it distinct and prominent.

The microscopic picture presented congestion and edema; some capillary hemorrhage; perivascular and also diffuse round cell infiltration; ganglion cells in various stages of destruction and neuronophagia; all the changes present in human cases, except that they are more severe.

Passage of this virus will be continued with the hope of increasing its virulence so as to permit to use filtrates in further work.

Appended is a chronologic table of protocols of the animal work here recorded.

SERUM THERAPY IN EXPERIMENTAL POLIOMYELITIS

The blood of persons who have survived an attack of acute poliomyelitis contains specific substances which possess the ability to neutralize active poliomyelitis virus. This has been demonstrated by Flexner and Lewis, Roemer, Landsteiner and Leviditi, and others. It has also been shown that monkeys recovering from an attack of poliomyelitis become refractory to a second inoculation of virulent material, and in the blood of these animals can be demonstrated the neutralizing principles found in the blood of recovered human cases.

Netter⁴³ applied this knowledge in the treatment of a small series of human cases, with perhaps favorable results. His conclusions were not very definite. He administered, intraspinally, from 4 to 12 c.c. of serum obtained from a recovered case whose blood yielded a negative Wassermann. It was administered daily for four or five days, or as

43. Netter: Bull. de l'Acad. de méd., 1914, 66, 525.

long as the clinical symptoms indicated its need. One case received eight injections.

Zingher,⁴⁴ of the Bureau of Laboratories, treated a larger number of patients by the intraspinal method, using serums obtained both from recovered cases of the disease and from normal persons. His report reads favorably to the treatment.

No tests were made to determine whether or not the serums obtained from the recovered patients possessed the neutralizing powers necessary to render it specific. Two cases of reinfection in the epidemic of the past summer, that had come to our attention, may throw some doubt on the assumption that all persons who recovered from one attack of the disease are immune to a second infection, or that the blood of all such persons possesses neutralizing powers.

The testing of the serum of each donor, however, for the specific principles would render the whole procedure impracticable, mainly because of the loss of time necessary to perform this test, and secondarily, because of the expense, for at the present time there is no way of demonstrating this property in serum, except by the injection into a monkey of active virus that had been placed in contact with the serum. From a practical point of view, the probabilities are that only a small percentage of the cases would give a negative test.

Schwartz⁴⁵ treated twenty-one patients with convalescent human serum. Of these, nine recovered without paralysis. Of a series of twenty-one other patients treated expectantly, seventeen recovered without paralysis. From this it might be inferred that the serum was of no particular advantage. Schwartz feels that too much was not to be expected of the use of the immune serum.

Prognosis in poliomyelitis is a difficult matter. Poliomyelitis is a very erratic disease and predictions as to the course it will follow in a given case are many times guess work. It will require, therefore, great numbers of cases adequately controlled to gain a true idea of the value of the serum treatment from the clinical point of view.

The clinical use of the serum of patients in old recovered cases of poliomyelitis is not founded on complete, clearcut animal experimentation. Its use is in part scientific, and in part empirical.

Flexner and Lewis⁴⁶ performed two experiments, the results of which indicate that a known specific serum may exert a prophylactic effect. An effective dose of active virus was injected intracerebrally into a monkey. Within twenty-four hours after the inoculation, and daily thereafter, the animal received intraspinal injections of immune

44. Zingher: *Arch. Pediat.*, 1916, **33**, 872.

45. Schwarz: *Arch. Pediat.*, 1916, **33**, 859.

46. Flexner and Lewis: *Jour. Am. Med. Assn.*, 1910, **54**, 1780, and **55**, 662.

serum for a number of days. This animal remained healthy, whereas the control died. Another monkey was inoculated by intranasal scarification with a potent virus. This animal received intraspinal injections of immune serum within twenty-four hours after the inoculation, and at three-day intervals for a number of injections. This monkey did not exhibit any symptoms of poliomyelitis, while the control died of the disease. The authors state that if the quantity of virus injected is not in excess of a certain amount, the procedure described will serve to protect animals injected with such a quantity of virus.

The conditions of these experiments, however, do not parallel those which are met with when dealing with actual human cases, in which the virus has already become established and is multiplying in the central nervous system, as evidenced by the symptoms of the disease. In this instance the specific serum no longer can prevent; it must cure. It must counteract and nullify virus that has already become parasitic and that may have increased in amount, perhaps in excess of that which can be taken care of by injections of known immune serum.

The present work in experimental serum therapy was undertaken in an attempt to supply the conditions that are met with in actual practice. This work comprises six experiments in each of which were used two animals. One animal was serum-treated and the other acted as a control. The virus was emulsion of brain and cord material derived from the epidemic of the past summer. Virus of the second generation was used in the first series, and the virus of each succeeding generation was used in the remaining experiments. The amount of virus injected was not determined from very much previous experience with this strain. That the dosage was not excessive is evidenced by the fact that two of the control animals, 37 and 54, and two others, 23 and 24, not used in these experiments, but which received the same amounts of virus, survived the disease.

The serum used in these experiments was obtained by heart-puncture from Monkeys 98 and 102. Both of these animals were resistant to the effects of three inoculations of brain and cord material. This material was inoculated in heavy suspensions intracerebrally, in the tissues about the sciatic nerves and in the peritoneum. The material for the first two inoculations was derived from two human cases, clinically and pathologically positive cases of poliomyelitis. The third inoculation was with material of the second generation monkey virus. These inoculations were given three weeks apart. It was assumed that as a result of these three inoculations, these monkeys were immune and that the blood of these animals ought to contain the specific antibodies. No neutralization test was performed on the serums used in this set of experiments. This, in a measure, parallels the clinical use of serum by Netter and Zingher.

In a series of experiments now under way we shall have the opportunity of observing the effects of known monkey and human immune serum in the experimental serum therapy of monkey poliomyelitis.

Method of Injection.—The serum was injected intraspinally by syringe in doses of 2 to 3.5 c.c., depending on the size of the animal and resistance offered to the plunger of the syringe. As much spinal fluid as possible was withdrawn, usually with the aid of the syringe. The first tap yielded up to 2 c.c. of slightly turbid fluid, but subsequent punctures yielded from 0.5 to 1 c.c. of fluid. The fluids, on being examined, when the quantity was sufficient, gave a globulin test and a definite increase in cells; in one instance, 690 cells per cubic millimeter. The serum was injected very slowly and with extreme caution against using any excess pressure. Only one animal exhibited severe effects after the intraspinal injection. These consisted of marked rigidity of limbs, retracted neck and labored and rapid respiration. They were, however, very transient and within a half hour after the injection the monkey appeared as before the injection. Retraction of the neck was noted after many of the injections, particularly after the symptoms of paralysis had appeared.

Time of Injection.—The time periods elapsing between the injection of the virus and the beginning of the intraspinal serum injections was so arranged as to be applicable to conditions met with in actual practice. In Experiments 1 and 2 the serum treatment was begun on the first day of the appearance of any muscular weakness. In the remaining four experiments serum treatment was instituted before any symptoms had appeared, corresponding to the pre-paralytic stage in the human disease.

The protocols are as follows:

EXPERIMENT 1.—Sept. 1, 1916. *M. rhesus* 50, injected with 0.5 c.c., intracerebrally, 2 c.c. perisciatric, and 10 c.c. intraperitoneally, of 10 per cent. suspension Generation II virus. *M. rhesus* 51, control, received 0.5 c.c., intracerebrally, of the same emulsion.

Sept. 6, 1916, No. 50 appeared sick and limped on left leg. Received 3.5 c.c. Serum 102, intraspinally. Sept. 7, 1916, 3.5 c.c. Serum 102, intraspinally. Limp still present. September 10 the limp was not noticeable and the animal appeared strong and healthy.

Sept. 5, 1916, *M. rhesus* 51, control, exhibited general tremors and marked muscular weakness; no definite paralysis. Died Sept. 8, 1916. Congestion of pia and swelling and reddening of gray matter of cord. The virus of this monkey subsequently produced typical flaccid paralysis.

Whether or not *M. rhesus* 50 really had poliomyelitis, it is difficult to judge. He did not at any time present frank paralysis and his rather rapid recovery is suspicious. This animal was one of whose past history we knew nothing.

EXPERIMENT 2: Sept. 21, 1916, *Rhesus* 27, 0.5 c.c. intracerebrally and 2 c.c. perisciatric, of 10 per cent. virus, Generation III; *Rhesus* 26, control, 0.5 c.c. intracerebrally, same virus.

Sept. 28, 1916, *Rhesus* 27; weakness left leg; 2.5 c.c. Serum 102 intraspinally. *Rhesus* 26, control; paralysis left, and weakness right leg.

Sept. 29, 1916, *Rhesus* 27, paralysis both legs; weakness left arm; 2.5 c.c. Serum 102, intraspinally. *Rhesus* 26, paralysis both legs; left arm; weakness right arm; difficulty in breathing.

Sept. 30, 1916, *Rhesus* 27, complete paralysis of limbs and diaphragmatic breathing. Died. *Rhesus* 26, respiratory failure. Died.

The incubation period in both of the animals was eight days and duration of illness three days.

EXPERIMENT 3: Oct. 2, 1916, *Rhesus* 36, 0.5 c.c. 10 per cent. virus, Generation IV, intracerebrally. *Rhesus* 37, control, 0.5 c.c. same suspension, intracerebrally.

Oct. 7, 1916, Rhesus 36, apparently normal; 3 c.c. Serum 102, intraspinally. Rhesus 37, well.

Oct. 8, 1916, Rhesus 36, well; 3 c.c. Serum 102. Rhesus 37, O. K.

Oct. 9, 1916, Rhesus 36, paralysis both legs; weakness left arm; 2.5 c.c. Serum 102. Rhesus 37, control; paralysis left leg; weakness right leg.

Oct. 10, 1916, Rhesus 36, complete paralysis both arms and legs; breathing with difficulty; no serum; condition bad. Rhesus 37, paralysis both legs; weakness left arm; does not appear as sick as 36.

Oct. 12, 1916, Rhesus 36, died of respiratory paralysis. Rhesus 37, paralysis of both legs; weakness left arm; cessation of progress of paralysis.

Nov. 29, 1916, Rhesus 37, alive; permanent paralysis in legs; left arm O. K.

In this experiment Rhesus 36 received serum treatment on the fifth day after injection of virus and two days before the onset of paralysis. Rhesus 37, control, exhibited paralysis on the same day as No. 36, an incubation of seven days. The serum treatment apparently had no influence on the incubation period. Furthermore, No. 36, despite three treatments, suffered a rapidly spreading, fatal form of the disease, whereas No. 37, control, survived the same injection, but with residual paralyses.

EXPERIMENT 4: Oct. 13, 1916, Rhesus 43, 0.5 c.c., 10 per cent., Generation V virus, intracerebrally. Rhesus 42, control, a very large animal, 1 c.c. intracerebrally and 5 c.c. intraperitoneally of same virus.

Oct. 18, 1916, Rhesus 43 received intraspinally, 3 c.c. Serum 102; October 19, 2.5 c.c. same serum; October 20, 3 c.c. Serum 102; October 21, 2.5 c.c. Serum 98; October 22, 2 c.c. Serum 98. No signs of disease during this period. Rhesus 42, control, presented no symptoms.

Oct. 23, 1916, Rhesus 43, left leg paralyzed and weakness in right leg; 2 c.c. Serum 98 given intraspinally. Rhesus 42 shows no symptoms.

Oct. 24, 1916, Rhesus 43, paralysis progressing; 2.5 c.c. Serum 102 administered. Rhesus 42 apparently well.

Oct. 25, 1916, Rhesus 43, paralysis involving both arms and legs; 3 c.c. Serum 102 given. Rhesus 42, control, shows weakness in left leg.

Oct. 27, 1916, Rhesus 43, died of respiratory paralysis. Rhesus 42 presents involvement of both legs and weakness of left arm.

Oct. 31, 1916, Rhesus 42 died of respiratory paralysis.

In the foregoing experiment, the serum treated animal began to receive intraspinal injections of serum on the fifth day after the injection of the virus and five days prior to the appearance of symptoms in the same animal, and seven days before the control animal exhibited muscular weakness. Furthermore, the control animal had several times the dose of virus received by the test animal. The progress of the disease was more rapid in the serum treated animal, which terminated on the fifth day of the disease, than in the control animal, which died on the seventh day of the disease.

EXPERIMENT 5: Nov. 2, 1916, Rhesus 52, 0.5 c.c. 10 per cent. Generation VI virus intracerebrally.

Oct. 31, 1916, Rhesus S, large animal, control, 0.5 c.c. intracerebrally and 5 c.c. intraperitoneally, of 10 per cent. Generation VI virus used on No. 52.

Nov. 8, 1916, Rhesus 52, apparently normal, received 2.5 c.c. Serum 102 intraspinally. Rhesus S, control, showed paralysis of left arm.

Nov. 9, 1916, Rhesus 52, paralysis of left leg; 2.5 c.c. Serum 102. Rhesus S, paralysis of all limbs and respiratory paralysis. Died.

Nov. 10, 1916, Rhesus 52, paralysis progressing; 2.5 c.c. Serum 102.

Nov. 11, 1916, Rhesus 52, paralysis of both legs and left arm; 2 c.c. serum 98 administered.

Nov. 13, 1916, Rhesus 52, complete paralysis, including muscles of respiration. Died.

Though Rhesus 52 received a smaller dose of virus and one injection of serum on the sixth day after the inoculation, the incubation period was seven days,

TABLE 21.—CHRONOLOGIC TABLE OF PROTOCOLS

No.	Species	Generation	Date of Injection	Inoculation, Days	Amount of Injection, C.c.	Strength, per Cent.	Site of Injection	Duration of Disease, Days	Character of Paralysis	Outcome
1	M. rhesus	I	8/12/16	7	0.5 2 5	20 20 20	Brain Periscapular Peritoneum	3	Progressing spinal, beginning in left leg	Died 8/22/16
10	M. rhesus	II	8/23/16	7	0.5 2 10	20 20 20	Brain Sciatic Peritoneum	3	Progressing spinal, beginning in left leg	Died 9/1/16
50	M. rhesus	III	9/ 1/16	4	0.5 2 10	10 10 10	Brain Sciatic Peritoneum	3	Slight weakness in left leg.....	Recovered with out paralysis
51	M. rhesus	III	9/ 1/16	4	0.5	10	Brain	8	General muscular weakness; murant type	Died 9/7/16
24	M. rhesus	IV	9/ 9/16	5	0.5	10	Brain	4	Progressing spinal, beginning in left leg; cessation of process; both legs and left arm involved	Recovered with residuals
26	M. rhesus	IV	9/21/16	7	0.5 (No. 51)	10	Brain	3	Rapidly progressing spinal, beginning with left leg	Died 10/10/16
27	M. rhesus	IV	9/21/16	7	0.5 (No. 51)	10	Brain	3	Rapidly progressing spinal, beginning with left leg	Died 10/1/16
36	M. rhesus	V	10/ 2/16	7	0.5	10	Brain	4	Rapidly progressing spinal, beginning with left leg	Died 10/12/16
37	M. rhesus	V	10/ 2/16	7	0.5	10	Brain	5	Progressing spinal, beginning with left leg; progressed as far as left arm	Recovered with residuals
25	M. rhesus	V	10/ 2/16	13	0.5	10	Brain	20	Slowly progressive spinal, beginning in left leg	Died 11/3/16
42	Giant M. rhesus	VI	10/13/16	12	0.5 5	10 10	Brain Peritoneum	7	Progressing spinal, left leg.....	Died 10/31/16
43	M. rhesus	VI	10/13/16	10	0.5	10	Brain	5	Progressing spinal, left leg.....	Died 10/27/16
S	M. rhesus	VII	10/31/16	8	0.5 5	10 10	Brain Peritoneum	2	Progressing spinal, left leg.....	Died 11/9/16
52	M. rhesus	VII	11/ 2/16	7	0.5	10	Brain	5	Progressing spinal, left leg.....	Died 11/13/16
53	Mangabey	VIII	11/10/16	7	0.5	5	Brain	6	Progressing spinal, beginning in right leg	Died 11/22/16
54	Mangabey	VIII	11/10/16	8	0.5	5	Brain	7	Progressing spinal, left leg, and weakness of right leg and left arm	Appears to be recovering
23	M. rhesus	VIII	11/15/16	11	0.5	10	Brain	4	Weakness of left and right legs.....	Appears to be recovering

TABLE 22.—SUMMARY OF EXPERIMENTS ON

No.	Species	Genera- tion	Virus Injected				Serum Injection Intraspiously		
			Amount, C.c.	Strength, per Cent.	Site	Date	Date	Amount, C.c.	Source, Serum
50	Rhesus	II	0.5 2 10	10 10 10	Brain..... } Sciatic..... } Peritoneum }	9/ 1/16	9/ 6 9/ 7	3.5 3.5	102 102
51	Rhesus Control	II	0.5	10	Brain	9/ 1/16
27	Rhesus	III	0.5 2	10 10	Brain..... } Sciatic..... }	9/21/16	9/28 9/29	2.5 2.5	102 102
26	Rhesus Control	III	0.5	10	Brain	9/21/16
36	M. rhesus	IV	0.5	10	Brain	10/ 2/16	10/ 7 10/ 8 10/ 9	3 3 2.5	102 102 102
37	Rhesus Control	IV	0.5	10	Brain	10/ 2/16
52	Rhesus	VI	0.5	10	Brain	11/ 2/16	11/ 8 11/ 9 11/10 11/11	2.5 2.5 2.5 2	102 102 102 98
S	Rhesus (large) Control	VI	0.5 5	10 10	Brain, intra- peritoneally	11/31/16
53	Mangabey	VII	0.5	5	Brain	11/10/16	11/15 11/16 11/18 11/19	3 3 2.5 2	102 102 98 98
54	Mangabey Control	VII	0.5	5	Brain	11/10/16
43	Rhesus	V	0.5	10	Brain	10/13/16	10/18 10/19 10/20 10/21 10/22 10/23 10/24 10/25	3 2.5 3 2.5 2 2 2.5 3	102 102 102 98 98 98 102 102
42	*Giant rhesus Control	V	1 5	10 10	Brain..... } Peritoneum }	10/13/16

INTRASPINAL TREATMENT WITH UNKNOWN "IMMUNE" SERUM

			Paralysis	Outcome
Date	Incubation, Days	Duration of Disease, Days	Character, Extent	
9/6	5	2	Slight weakness in left leg.....	Alive and well
9/5	4	3	General muscular weakness; marantic type.....	Died 9/8/16
9/28	8	3	Rapid progressive paralysis, left leg, right leg, left arm and right arm; resp. failure	Died 9/30/16
9/28	8	3	Rapid progressive paralysis, left leg, right leg, left arm, right arm; resp. failure	Died 9/30/16
10/9	7	4	Rapid progressive paralysis beginning with left leg; right leg, left arm, right arm; resp. paralysis	Died 10/12/16
10/9	7	4 acute	Progressive flaccid paralysis beginning with left leg; right leg, left arm, then regression	Alive; has diplegia
11/9/16	7	5	Progressive spinal, beginning with left leg; then right leg, left arm, right arm	Died 11/13/16
11/8/16	9	2	Rapid progressive spinal, beginning with left arm; then right, then resp. failure	Died 11/9/16
11/7/16	7	6	Progressive spinal paralysis, beginning with right leg; then left leg, left arm, right arm; resp. failure	Died 11/22/16
11/18/16	8	8	Progressive spinal paralysis, beginning with left leg; weakness right leg and left arm; slight weakness in right arm	Alive and improving
10/23/16	10	5	Progressive flaccid paralysis beginning with left leg, then right leg, then left arm, then right arm; resp. failure	Died 10/27/16
10/25/16	12	7	Progressive spinal paralysis, beginning with left leg, then right leg; simultaneously in both arms; resp. failure	Died 10/31/16

whereas in Rhesus S, with larger dosage, and no serum therapy, the incubation was nine days. This animal, however, suffered a fulminating type of disease, dying on the second day after the appearance of symptoms. This was probably due to the early involvement of muscles of respiration. The serum treated animal died on the fifth day of the disease.

EXPERIMENT 6: Nov. 10, 1916, Mangabey 53, 0.5 c.c. 5 per cent. Generation VII virus, intracerebrally. Mangabey 54, control, 0.5 c.c. 5 per cent same virus, intracerebrally.

Nov. 15, 1916, Mangabey 53, appears well; 3 c.c. Serum 102, intraspinaly.

Nov. 16, 1916, Mangabey 53, 3 c.c. Serum 102, appears normal.

Nov. 17, 1916, Mangabey 53, paralysis of left leg; no serum.

Nov. 18, 1916, Mangabey 53, paralysis progressing; 2.5 c.c. Serum 98. Mangabey 54, weakness left leg.

Nov. 19, 1916, Mangabey 53, paralysis both legs and left arm; 2 c.c. Serum 98 administered. Mangabey 54, marked weakness in left leg and slight weakness in right leg; progress of paralysis slow.

Nov. 20, 1916, Mangabey 53, lies prone; does not stir body; moves right arm weakly; tremor of head. Mangabey 54, condition about the same as before.

Nov. 22, 1916, Mangabey 53, complete paralysis. Died. Mangabey 54, weakness in legs more marked.

Nov. 25, 1916, Mangabey 54, progress of involvement slow; shows slight weakness of left arm; tremor of head.

Nov. 27, 1916, Mangabey 54, shows signs of improvement; left arm apparently stronger, as is also the right leg.

Dec. 1, 1916, Mangabey 54, improvement marked; feeds well; can sit up without great difficulty; will probably recover.

In the foregoing experiment the test animal received serum treatment on the fifth day after the injection of virus and two days before symptoms of the disease appeared in an incubation of seven days. The disease ran a progressive, fatal course despite four injections of serum. The control animal showed evidence of paralysis on the eighth day after infection, with slowly progressing symptoms and with subsequent improvement. This animal is alive at this writing.

Summary.—A summary of the results of the foregoing experiments is as follows:

Five of the six serum-treated animals died, a mortality of 83 per cent. Four of the six control animals died, a mortality of 66 per cent. Of the four animals that received intraspinal serum therapy before the appearance of paralysis, one received one treatment, two received two treatments and one five treatments in the preparalytic stage. In one of these, the incubation period was the same as in the control animal. In the remaining three, the incubation was shorter by one to two days than in the control animals. The duration of the disease in the serum treated animals was somewhat shorter than in the controls, varying from two to six days, whereas in the latter, the acute progressive stage was from three to eight days, indicating a greater rapidity in the spread of the disease in the central nervous system. The number of serum administrations varied from two to eight, depending on the condition of the animal. They were discontinued when the animal exhibited distinct signs of improvement, or when the paralysis had progressed to respiratory difficulty.

DISCUSSION

Experimental poliomyelitis is several times more fatal a disease than human poliomyelitis, and perhaps it is rather severe on the clinical use of untested "immune" serum to compare it with experimental use of a like serum in monkey poliomyelitis. That, however, seems to be the only method known at the present time of gaining any correct

idea of the value of this method of treatment. An effort was made in the foregoing experiments to parallel clinical conditions. Two of the animals were injected with serum on the first day of the appearance of paralysis and four from five to six days after the date of infection, but in the preparalytic stage. The test animals were controlled by six animals that received no serum therapy.

Comparison of the effects of the disease in the serum-treated animals as against the effects observed in the control animals, would incline one to the inference that, at least in the experimental disease, intraspinal injections of serum are not only of no value, but also that there may be in them an element of harm. The mechanism producing the untoward effects has not been demonstrated as yet, but it may consist in the exaggeration of the pathologic process already existing by the introduction into the subdural space of a foreign substance. Marked meningeal symptoms have been observed following the introduction of serum, both in the experimental and human disease. In some instances, the spinal fluids obtained after the injection of serum have shown distinct evidences of accentuated inflammatory reaction, as indicated by increased turbidity, due to increase of cellular elements and increase in the content of albumin and globulin.

That this meningeal reaction may have a deleterious influence on the already existing pathologic process in the cord and brain proper, is not without plausibility.

Careful comparative study of the nervous tissues of the serum treated and the control animals may indicate whether or not this is the true explanation.

FURTHER STUDIES WITH THE SCHICK TEST*

ABRAHAM ZINGHER, M.D.

Assistant Director, Research Laboratory

NEW YORK

* The Schick test has found considerable favor as a reliable clinical test in showing the presence of immunity or susceptibility to diphtheria, and is being used more and more by a rapidly increasing number of physicians. The test is now employed as a routine procedure in a great many institutions, hospitals, and in the private practice of numerous physicians. Not only is the test used to indicate the immunity of the children, but it is also of great value in active immunization with diphtheria toxin-antitoxin. For this purpose the Schick test is used not only to select the susceptible individuals, but also to indicate the efficiency and the duration of the active immunity. The very reliability of the Schick test when carefully carried out, indicates that, in making the test, one should take definite precautions to use a toxin of standard strength and carefully observe the exact directions for technical details.

Occasionally, however, the interpretation of the test, especially of the pseudoreaction, is quite puzzling to some physicians. When the test is either positive or negative, there is, as a rule, no difficulty in reading the reaction. It is only with the pseudoreaction and the combined reactions that some little difficulty may be experienced unless one is guided by a knowledge of the clinical course of these false reactions.

The pseudoreaction depends on a hypersusceptibility of the tissue cells of individuals to the autolyzed protein of the diphtheria bacillus, which is present in the toxin broth used for the test. The reaction is, therefore, of the nature of a local anaphylactic response. Clinically, the pseudoreaction is distinguished from the positive reaction by its rather rapid development. It appears usually within twelve to eighteen hours, reaches its height in twenty-four hours, and fades in about three to four days, leaving only an irregular area of brownish pigmentation and generally shows no scaling. In appearance the moderate pseudoreactions at the end of twenty-four hours resemble very much the fully developed positive reactions, while the marked pseudoreactions show a considerable amount of infiltration, with a central darker reddish area, surrounded by a fainter areola, which shades off into the surrounding skin. To make a final reading of the Schick test at the end of twenty-four hours, therefore, is fraught with the danger of confusing the true with the pseudoreactions.

* Submitted for publication April 6, 1917.

* From the Research Laboratory, Department of Health.

To exclude the pseudoreactions two methods are open:

(a) One is to make the test and wait three to four days before the final observation. By this time the pseudoreaction generally will have faded and can be recognized by a blotchy area of pigmentation, while the true positive reaction will be at its height. The positive reaction will show at this time a definite circumscribed area of scaling redness, which gradually develops a brownish pigmentation. Those tests, however, which show only areas of bluish discoloration, or faded irregular areas of brownish pigmentation which do not scale, are generally the remains of pseudoreactions. These reactions were at their height at the end of twenty-four hours. It is important not to mistake them, when seen at the end of seventy-two hours, for faintly positive Schick tests. Where doubt exists, it is better to make a control test with heated toxin and observe the reaction at the end of twenty-four hours.

(b) A second method, which has certain very definite advantages, consists in using as a control on the opposite forearm at the same time the Schick test is made, a solution of diphtheria toxin which has been heated to 75 C. for five minutes.¹

By heating the toxin broth at this temperature the soluble toxin is destroyed, while the autolyzed protein of the diphtheria bacillus, which causes the pseudoreactions, is not appreciably affected. The control test with the heated toxin will reveal the pseudoreaction and combined reactions. Observations must be made at the end of twenty-four hours, and again at the end of seventy-two or ninety-six hours. The twenty-four-hour reading will give fairly accurate results in about 95 per cent. of the tests, when the *control test* with heated toxin has also been made. If *negative*; both the test and control will be normal. If a *pseudoreaction* is present, both the test and the control will show areas of redness and infiltration, which are similar in size and appearance; both reactions will fade at the end of seventy-two hours and leave only a small irregular area of pigmentation, and generally no scaling. The pseudoreaction varies in intensity in different individuals from an area of circumscribed redness without infiltration to a reaction which shows a considerable degree of redness and infiltration, and a more or less characteristic clinical appearance.

If a *combined* reaction is present, the redness and infiltration at the site of the Schick test will be more marked at the end of twenty-four hours than in the control test. At seventy-two hours the positive reaction will be quite distinct, while the control test will show only a blotchy

1. Zingher, Abraham: The Pseudoreaction in the Schick Test and Its Control, Jour. Am. Med. Assn., 1916, **66**, 1617.

area of pigmentation representing the pseudoreaction elements of the test. If the test is *positive*, the reaction at the end of twenty-four and seventy-two hours will be positive only at the site of the Schick test. The *negative* and the *pseudoreactions* indicate immunity, the *positive* and the *combined* reactions, susceptibility to diphtheria.

The Schick test and the control test were made on all the inmates of two institutions, the New York Foundling Hospital and the Dominican Convent. In addition to noting the frequency and character of the pseudoreactions, some interesting observations were made at the first institution on certain phases of natural immunity, transmission of immunity from mother to offspring, and the duration of the passively acquired immunity in the infant.

I. OBSERVATIONS AT THE NEW YORK FOUNDLING HOSPITAL

In this institution we had opportunity not only to test some 500 children of varying ages, but also to make comparative observations on ninety-three mothers and their infants. Von Gröer and Kassowitz² have shown that mothers and their new-born infants reveal, as a rule, a similar antitoxin content. If present, the antitoxin in the infant's circulation is probably derived from the mother through the placenta. The immunity of the infant is temporary, lasting from four to six months.

Tables 1 to 3 give summaries of the results noted in this institution.

TABLE 1.—SUMMARY OF RESULTS WITH THE SCHICK TEST AND CONTROL TEST AT THE NEW YORK FOUNDLING HOSPITAL

	Immunes			Nonimmunes			Total Tested	Per Cent. Pseudo	Per Cent. Positive and Combined
	Negative	Pseudo	Total	Positive	Combined	Total			
Children, 0 to 8 yrs. ...	854	23	877	140	2	142	519	4.4	27.5
Adults.....	59	48	102	6	5	11	118	38.0	9.7
Total.....			479	153	632		

In Table 1 it is interesting to note the relatively small number of pseudoreactions in children up to 8 years of age (4.4 per cent.) and the relatively large number in adults (38.0 per cent.), as compared with the positive Schick tests, of which the children (27.5 per cent.) have nearly three times as many as the adults (9.7 per cent.).

2. Von Gröer, F., and Kassowitz, K.: Studien über die normale Diphtherieimmunität des Menschen, II. Ueber das Verhalten des normalen Diphtherieantitoxins bei Mutter und Neugeborenen. Ztschr. f. Immunitätsforsch. u. exper. Therap., 1914. Orig., 23, 108-126.

TABLE 2.—SUMMARY OF SCHICK TESTS BY AGE GROUPS

Age	Total	Negative	Positive	Per Cent. Pos.
0 to 6 months.....	101	82	19	18.0
6 to 12 months.....	84	40	44	52.3
1 to 2 years.....	52	28	24	46.1
2 to 4 years.....	127	82	45	35.8
4 to 6 years.....	103	88	20	18.5
6 to 8 years.....	25	22	3	12.0
Total.....	407	342	155	31.2

Table 2 shows that the largest proportion of positive Schick reactions was found between the ages of 6 months and 4 years. The positive reactions diminish rapidly after the fourth year of life.

TABLE 3.—COMPARATIVE RESULTS WITH SCHICK TEST IN MOTHERS AND INFANTS

Ages of Infants, Months	A		B		C		D	
	Mother Neg.	Schick Neg.	Mother Neg.	Schick Pos.	Mother Pos.	Schick Pos.	Mother Pos.	Schick Neg.
Up to 3	18		1		4		0	
3 to 6	10		2		2		0	
6 to 9	9		11		1		0	
9 to 12	2		10		..		0	
12 to 15	4		6		..		0	
15 to 24	2		2		..		0	
Total	54		32		7		0	

In Table 3 the following interesting points may be noted:

1. The antitoxic immunity in the infant, obtained from the immune mother, lasts for about six months after birth. Column A shows that thirty-seven out of fifty-four infants, or 68.5 per cent., continued to show a negative test during the first half year of life. The negative test in the nine children between 6 and 9 months of age is probably due to a continuation of the passive immunity derived from the mother, while in the remaining eight children we are probably dealing with an early developed natural antitoxic immunity. A definite solution of this question can only be obtained by repeated Schick retests; the children who were still passively protected would lose their antitoxin in the course of a few months and then give a positive reaction, while those with an early developed natural immunity would continue to give a negative Schick test.

2. Column B shows that a large proportion of children belonging

to immune mothers has positive Schick tests after the sixth month of life. Twenty-seven out of thirty-two children between 6 and 15 months, or 86.2 per cent., gave a positive Schick test.

3. In Column C, seven children are shown who gave a positive reaction, and whose mothers also gave positive reactions. The results indicate definitely that where a mother has no immunity, none will be present in her infant if it is below 6 months of age.

4. Column D shows that no case was found in which the mother had a positive and the young infant a negative Schick test.

II. OBSERVATIONS AT THE DOMINICAN CONVENT

TABLE 4.—SUMMARY OF RESULTS WITH SCHICK TEST AND CONTROL TEST AT THE DOMINICAN CONVENT

Age	Immunes			Nonimmunes			Total Tested	Per Cent. Pseudo	Per Cent. Positive and Combined
	Negative	Pseudo	Total	Positive	Combined	Total			
4 to 6 years	29	8	37	14	1	15	52	15.4	28.4
6 to 8 years	446	14	60	6	1	7	67	20.8	10.4
8 to 10 years	13	12	25	4	3	7	32	37.5	21.8
10 to 15 years	42	25	67	2	2	4	71	35.2	5.6
Total	130	59	189	26	7	33	222	26.5	14.8

Two hundred and twenty-two children varying in age from 4 to 15 years were tested with the Schick test and the control test. Table 4 gives a summary of the results. In the lower line we see that among all the children the positive and combined reactions indicating the non-immunes were thirty-three, or 14.8 per cent., the combined reactions representing about one-fifth of the total nonimmunes. Among the 189 immunes there were fifty-nine pseudoreactions, or a little less than one-third. The percentage of pseudoreactions among all the children tested was 26.5 per cent.; the individual age groups vary, the table showing that the pseudoreactions increase rapidly after the eighth year, and are very frequent, especially among females, after the twelfth year of life. This holds especially true for the stouter individuals, who frequently give pseudoreactions.

The relatively high proportion of pseudoreactions in older children and in adults indicates the necessity of using the control test with heated toxin. Where accurate readings are needed, especially in active immunization with toxin-antitoxin, or where the Schick test has to be read within twenty-four or forty-eight hours, the control test with heated toxin will be found of great assistance.

III. OBSERVATIONS IN OTHER INSTITUTIONS

TABLE 5.—SUMMARY OF SCHICK TESTS AT THE NEW YORK CATHOLIC PROTECTORY

Age	Total	Negative	Positive	Per Cent. Pos.
4 to 6 years.....	126	113	13	10.3
6 to 8 years.....	212	202	10	4.7
8 to 10 years.....	91	82	9	9.9
10 to 15 years.....	233	220	13	5.5
15 years up.....	25	24	1	4.0
Total.....	687	641	46	6.7

TABLE 6.—SUMMARY OF SCHICK TESTS AT THE INSTITUTE OF MERCY

Age	Total	Negative	Positive	Per Cent. Pos.
4 to 6 years.....	62	54	8	12.9
6 to 8 years.....	62	52	10	16.1
8 to 10 years.....	47	41	6	12.7
10 to 15 years.....	151	141	10	6.6
Total.....	322	288	34	10.5

The relatively small number of positive Schick tests in other institutions, where children ranging in age from 4 to 14 years were tested, may be seen from Tables 5 and 6. In these institutions the Schick test was made without a control. The tests were read at the end of four days, and the pseudoreactions identified by the irregular blotchy area of bluish or brownish discoloration. They are included in these tables under negative Schick reactions. Table 5 shows an average of not more than 6.7 *per cent.*, and Table 6, 10.5 *per cent.* of positive Schick reactions.

TABLE 7.—SUMMARY OF RESULTS WITH SCHICK TEST AT ST. JOSEPH'S INSTITUTE

Age	Immunes			Non-immunes, Positive	Total Tested	Per Cent. Pseudo	Per Cent. Positive
	Negative	Pseudo	Total				
(a) Boys							
5 to 10 years.....	48	0	48	7	55	0.0	12.7
10 to 15 years.....	103	8	111	1	112	7.1	0.9
15 to 20 years.....	39	11	50	1	51	21.5	1.9
Total.....	190	19	209	9	218	8.7	4.1
(b) Girls							
5 to 10 years.....	24	1	25	11	36	2.8	30.6
10 to 15 years.....	49	11	60	9	69	15.9	13.0
15 to 20 years.....	28	11	39	4	43	25.6	9.3
Total.....	101	23	124	24	148	16.2	15.5

Table 7 shows the results with the Schick test at St. Joseph's Institute. No control tests were made. The reactions were read at the end of four days, the pseudoreactions being differentiated from the true reactions by their clinical course and appearance. It is interesting to note that among the 218 boys not more than 4.1 *per cent.* gave a positive Schick test, while 8.7 *per cent.* gave a pseudoreaction. Among the girls, the number of positive Schick tests (15.5 *per cent.*), and the number of pseudoreactions (16.2 *per cent.*), was much higher than among the boys.

These low percentages of nonimmunes among children over 5 years of age explain the relative infrequency of diphtheria outbreaks in many institutions. They also represent, however, an encouraging factor in greatly limiting the total number of children that would need to be actively immunized against diphtheria.

If an outbreak of diphtheria occurs in such an institution, the non-immunes can be easily selected by the Schick test for passive immunization. A considerable saving of antitoxin can be thus effected, and the unnecessary sensitization of a large number of children, with the frequently disagreeable after-effects, avoided.

SUMMARY AND CONCLUSIONS

1. The number of pseudoreactions varies in different age groups, but is considerable after the eighth year of life.

2. The intensity of the pseudoreaction varies from a simple redness to a reaction showing marked redness and infiltration.

3. For accurate work, or where the test is to be read at the end of thirty-six to forty-eight hours, the control test with heated toxin is important.

4. The antitoxin immunity which an infant derives from its mother lasts for about six months after birth. The Schick test illustrates in a very definite way the protection against diphtheria which an infant enjoys during the first half year of life.

5. Where the mother gives a positive Schick test, her infant will also generally show a positive test during the first six months of life. Where the mother gives a pseudoreaction, the infant, if young enough, will as a rule show a negative and not a pseudoreaction. The susceptibility of the tissue cells to the bacillus protein, which gives the pseudoreactions, is not transmitted from mother to offspring.

6. The largest number of positive Schick reactions is found in children between 6 and 18 months of age. This is therefore the best time, not only to test the children, but also actively to immunize with toxin-antitoxin those who show a positive reaction.

I wish to thank Dr. Charles D. Jones for his valuable assistance in two of the institutions, and Dr. A. E. Schreïbman for his cooperation in the work at the New York Foundling Hospital.

420 West End Avenue.

THE EFFECT OF UNDERNUTRITION ON MUSCULAR FORCE

A STUDY OF THE INFLUENCE OF LOW DIETS, OR THE ALLEN METHOD OF
TREATMENT ON THE PHYSICAL VIGOR
OF DIABETICS *

JOHN R. WILLIAMS, M.D.
ROCHESTER, N. Y.

As is now generally known, the cardinal features of the Allen method of treating diabetics are fasting, and the feeding of low diets and diets so modified as to meet the metabolic needs of the individual. While fasting and low feeding have been suggested and employed by various other workers in this field, the persistent and continued use of these dietary measures to the point of making and maintaining the patient both acid and sugar free, as employed by Allen, is a radical departure from former methods of treatment.

Among the many fears which this unique treatment has excited in the minds of both clinicians and patients is that the persistent use of the low diet would gradually and seriously weaken the patient. Untreated diabetics are accustomed to eating even larger quantities of food than are normal individuals. The diet of normal individuals of course varies widely with the age and is influenced greatly by such factors as sex, habit and occupation. Few healthy persons, however, eat less than 1,500 calories per day, many eat as much as 4,000 calories per day, and the normal range may be considered as between 2,000 and 3,000 calories. According to Lusk,¹ "the average starvation metabolism of a vigorous man at light work and weighing 70 kilograms, approximates 2,240 calories, or 32 calories per kilogram, and the maintenance requirement is between 11.1 and 14.4 per cent. above the starvation minimum. This would amount to from 2,488 to 2,562 calories, or from 35.5 to 36.6 calories per kilogram of body weight in the case of the individual just referred to." It is quite generally accepted that the healthy adult individual needs, for the proper maintenance of weight and physical vigor, about 40 calories of food per kilo of body weight, and growing children from 50 to 90 calories per kilo of body weight.

All recent studies show that few diabetics can tolerate much more than half these quantities of food. In some mild cases the patients

* Submitted for publication April 19, 1917.

1. Lusk, Graham: *The Science of Nutrition*, 1909, p. 210.

improve to the degree that between 2,000 and 2,500 calories can be eaten without provoking a glycosuria; in the majority of mild cases they do better, however, on diets ranging between 1,500 and 2,000 calories per day.

In advanced cases the patients are obliged to live on less food in order to remain sugar free. It is common to find patients who can tolerate not more than 1,000 calories per day, and there are numerous instances of individuals who have had to live on less (Table 1).

TABLE 1.—FOOD TOLERANCE IN DIABETICS

Showing total food tolerance in calories of a series of diabetic patients when discharged from the hospital, who still survive. The urine of each patient was free of both sugar and ketone bodies.

Total Calories in Diet	Number Males Over 15 Years	Number Females Over 15 Years	Children Under 15 Years	
			Males	Females
700.....	4	1	0	1
800.....	0	1	0	0
900.....	1	2	0	0
1000.....	1	2	0	0
1100.....	2	3	1	1
1200.....	4	1	1	1
1300.....	0	7	0	0
1400.....	1	3	0	0
1500.....	4	5	0	0
1600.....	1	3	2	0
1700.....	5	7	1	0
1800.....	9	0	1	0
1900.....	4	1	1	0
2000.....	4	0	0	0
2100.....	3	0	0	0
2200.....	1	0	0	0
2400.....	2	0	0	0
Total cases	46	36	7	3

COMMENT.—It will be seen that 4 males and 1 female over 15 years of age and 1 female under 15 years of age, in order to remain sugar and acid free, were compelled to live on diets approximating 700 calories. Likewise 4 males and 1 female over 15 years of age, and 1 male and 1 female under 15 years of age had dietary limitations of 1,200 calories, and so on. This table illustrates very well the caloric tolerance of diabetic patients who are favorable for treatment, and it affords a fairly reliable measure of the deprivation which they must undergo. These diets range from 5 to 40 per cent. under the supposed minimum starvation metabolism requirements.

In the minds of many clinicians the question has arisen, What effect does the persistent use of a low diet have on the physical vigor of the diabetic? The fear is often expressed that its continued use must eventually exhaust the patient. Muscular weakness is one of the commonest symptoms of the disease; therefore the influence of under-feeding is a pertinent question and worthy of consideration.

During the past year the writer has endeavored to gain some tangible evidence on this point. At the suggestion of Dr. Aleš Hrdlička,

TABLE 2.—DYNAMOMETER TESTS

Case 1522; male, aged 18. Table showing a comparison over a long period of time of the total calories in the diet, weight, urine and lung air findings with the measure of muscular force as determined by tests of grip strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO ₂ in Lung Air, Mm.
				Sugar, Gm.	NH ₃ , Gm.	
397	1,700	142½	R 36 - L 24	25	1.48	38.6
402	1,310	142½	R 37 - L 30	0	0	44.6
409	1,535	146	R 36 - L 32	0	0	40.0
415	1,585	146	R 38 - L 32	0	0	43.2
421	1,585	145	R 38 - L 30	0	0	—
430	1,585	147	R 36 - L 30	0	0	44.5
437	1,600	147	R 40 - L 32	0	0	38.7
759	1,640	142½	R 46 - L 34	0	0	45.1

COMMENT: Case 1522 presents interesting features. The patient left the hospital after a stay of twenty-one days on a diet approximating 1,800 calories. This he increased rapidly by the addition of fat to 2,500 calories. The excessive fat apparently produced a cholesterinemia and was subsequently reduced to about 1,800 calories. The patient suffered from two serious "grippe colds," which for several weeks made it necessary for him to live on a diet ranging from 600 to 1,200 calories. One of these infections immediately preceded the period covered by the data in Table 2. It will be seen that while this patient's weight remained fairly constant, he gained considerably in muscular force, although he had been on a diet averaging 1,600 calories, considerably below the figures given by Lusk for the average starvation metabolism of a man doing light work, which in this patient's case would amount to 2,080 calories. It will be noted that this patient had been under treatment and on a comparatively low diet for more than two years. At the date of the last examination, he presented the usual evidences of physical vigor observable in a young man, and these observations are confirmed by an increase in his muscular force as measured by the strength of grip which, it will be noted, is well within the normal range. There are no evident reasons for thinking that this patient has in any way suffered because of the long period of undernutrition to which he had been subjected; on the contrary, it is highly probable that a serious diabetic condition has been ameliorated and a metabolic collapse averted.

assistant curator in charge of the Division of Anthropology, United States National Museum, Washington, a Collin dynamometer was used for the purpose. With this instrument the maximum pressure which can be exerted by each hand can be determined. This test, also known as the strength of grip, is used by psychologists and anthropologists as an index of general bodily strength. According to Hrdlička,² adult

TABLE 3.—DYNAMOMETER TESTS

Case 1881; girl, aged 16. Table showing a comparison of the total calories in the diet, weight, urine and lung air findings with the measure of muscular force as determined by tests of grip strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO ₂ in Lung Air, Mm.
				Sugar, Gm.	NH ₃ , Gm.	
2	30	90	R 15 - L 14	0.57	29.5
3	205	90	R 17 - L 15	1.17	29.5
4	226	87½	R 16 - L 15	0.94	28.8
5	312	85½	R 15 - L 12	1.29	29.5
6	445	85½	R 16 - L 14	1.20	39.8
7	670	86¾	R 18 - L 17	0.87	36.9
8	683	86¾	R 16 - L 15	40.4
9	874	87	R 18 - L 16	38.0
11	814	85½	R 16 - L 16	35.6
12	1,034	85½	R 17 - L 15	34.9
13	1,034	85¼	R 19 - L 17	43.4
14	1,161	85¼	R 17 - L 16	39.6
16	1,334	85	R 21 - L 16	37.2
22	1,696	85¾	R 30 - L 18	41.9

COMMENT: Diabetes was discovered in this child three months before entering the hospital. During this period she was alternately starved and overfed. Weakness was an important symptom. After the sixth day she was required to take systematic dumbbell exercise daily, together with walks in the fresh air. The test of muscular force confirms the striking improvement in the child's physical condition.

healthy American-born whites give records ranging, for pressure in the right hand, in males, from 35 to 60; in females, from 25 to 38 kg.; for pressure in the left hand, in males, from 30 to 50; in females, from 20 to 30 kg. A healthy right-handed white man from 25 to 40 years

2. Hrdlička, Aleš: Physiological and Medical Observation Among the Indians of Southwestern United States and Northern Mexico, Bureau of American Ethnology, Bull. 34, p. 143.

of age, used to some muscular work or exercise, will press with the right hand 50 to 55, with the left hand 40 to 45 kg.; a healthy right-handed white woman between similar limits of age and with good muscular tone, can press with the right hand from 30 to 35, and with the left hand 20 to 30 kg. As age advances, the muscular force in general becomes gradually less.

The test of muscular force was made in the following manner: In each instance a Collin dynamometer was used. Tests were made in

TABLE 4.—DYNAMOMETER TESTS

Case 1517; girl, aged 17. Table showing a comparison of the total calories in the diet, body weight, urine and lung air findings, with the measure of muscular force as determined by tests of grip strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO ₂ in Lung Air, Mm.
				Sugar, Gm.	NH ₃ , Gm.	
127	990	95	R 18 - L 11	8	0.75	33.2
128	895	95	R 18 - L 14	0	0	34.9
129	895	93	R 19 - L 11	5	0.43	36.1
140	915	93	R 18 - L 12	13	0.60	40.0
142	878	93	L 19 - L 12	10	0.27	37.8
143	100	93	R 18 - L 16	0	2.24	—
144	530	94	L 21 - L 19	0	2.19	38.9
145	485	93½	R 22 - L 18	4	0.61	30.0
146	670	92	R 22 - L 17	8	0.92	38.0
147	100	93	R 22 - L 17	0	2.20	33.3
148	802	94	R 19 - L 18	0	1.80	37.8
151	712	92	0	1.53	37.8
159	355	93	R 24 - L 17	0	0.58	—
161	975	91½	R 22 - L 17	0	0	41.7

COMMENT: This young woman had a serious diabetes for nearly one year before it was discovered and before treatment was instituted. It will be observed that on the 127th day of her treatment, when the observations on muscular force in her case were begun, she was well advanced. This persistent low metabolic state the writer attributes to a persistent chronic infection which was localized beneath a very expensive piece of dental bridge work, and which the parents were unwilling to have removed. In spite of her very low diet, this patient lost very little in weight and maintained to a surprising degree her physical vigor, as evidenced by the strength tests. This patient led an active outdoor life, playing tennis mildly, and indulging in other forms of recreation. Shortly after the date of the last observation, already noted, the patient abandoned the treatment, ate indiscriminately, rapidly lost in weight and strength and a few months later died. This case illustrates the fact that a patient, even on a very low diet suited to the metabolic needs of the individual, may gain in physical vigor, and that a diet in excess of these limitations may cause loss of physical strength and even death.

the morning. The spirit of competition was encouraged among patients so as to excite their best efforts. Two or three trials were made with each hand and the best effort recorded. The Collin dynamometer is graduated to read in kilograms. On the clinical charts and in the tabulations accompanying this paper, R 25-L 20 means that with the right hand the patient registered 25 kilograms, and with the left hand 20 kilograms. The dial should be held toward the palm with the little set screw between the fingers. This ensures a more accurate reading and avoids hurt to the hand. The tests, where possible, were made with the patient in a standing position, with the arms held away from the body and not supported in any manner. These precautions are

TABLE 5.—DYNAMOMETER TESTS

Case 1787; woman, aged 52. Table showing a comparison of the total calories in the diet, body weight, urine and lung air findings, with the measure of muscular force as determined by tests of grip of strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO ₂ in Lung Air, Mm.
				Sugar, %Gm.	NH ₃ , Gm.	
3	55	138	R 15 - L 11	6	1.30	34.3
11	695	134	R 20 - L 16	9	1.65	37.5
19	1,233	132½	R 17 - L 14	0	0.87	42.1
109	30	135	R 20 - L 19	..	0.71	
112	1,100	135	R 22 - L 18	..	0.61	
114	1,000	134	R 26 - L 20	3	0.90	
115	900	134	R 25 - L 19			

COMMENT: Diabetes was discovered in this patient six months before the date of the foregoing observations. The chief symptom was weakness. It will be noted that the patient had a mild acidosis when she entered the hospital. During the 115 days in which she was more or less under observation, she lived on not more than 60 per cent. of the total calories thought necessary to maintain her minimum metabolism, yet she gained noticeably in physical vigor, as is evidenced by her strength tests.

necessary for accurate results. Tests of patients who are unduly worried or after sleepless nights are of value as indicating the depressing physical effect of anxiety and dissipation, and may prove misleading unless properly interpreted. They should be used guardedly in measuring the normal muscular force of patients. This was well illustrated in one of the cases studied, a sturdy male of 57 years. This man was able repeatedly to exert a pressure of 36 kilograms with his right hand and 26 with his left hand. On the day after he was told

that his blood gave a marked positive Wassermann reaction and its significance, and after twenty-four hours of worry, the greatest pressure he could exert with his right hand was 28 kilograms and with his left, 22 kilograms.

TABLE 6.—DYNAMOMETER TESTS

Case 1680; woman aged 19. Table showing a comparison over a period of 598 days of the total calories in the diet, body weight, urine and lung air findings, with the measure of muscular force as determined by tests of grip of strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO ₂ in Lung Air, Mm.
				Sugar, Gm.	NH ₃ , Gm.	
390	140	120	R 18 - L 14	0.84	44.0
523	565	103	R 10 - L 12	0	35.6
526	982	104½	R 12 - L 9	0		
537	1,248	100	R 15 - L 12	Trace	43.0
544	978	99½	R 12 - L 11	Trace	42.9
549	1,105	103	R 12 - L 12	Trace	0.53	43.2
557	498	99	R 12 - L 10	Trace	38.5
568	1,234	100	R 14 - L 9	Trace	0.15	44.1
575	1,303	101½	R 15 - L 10	Trace	0.47	42.5
582	1,165	100	R 16 - L 11	44.9
587	1,436	101	R 12 - L 10	0	0.54	
594	1,350	98½	R 12 - L 9	0.44	38.7
598	1,429	98½	R 15 - L 11	0	0.49	43.0

COMMENT: This case presents most unusual features. Diabetes was discovered in this young woman in May, 1915. She entered the hospital for treatment in July, 1915. After a stay of one month she went home, sugar and acid free, on a diet of about 2,000 calories. Events subsequently proved that she was being overfed on fat and this was reduced. From Nov. 1, 1915, to Jan. 1, 1917, she lived on a diet averaging under 1,000 calories; much of the time it was less than 800 calories. At one time, omitting the fat entirely from the diet served to increase her carbohydrate metabolism from 20 to 70 gm. About Dec. 1, 1916, it became almost impossible to keep her sugar free when any carbohydrate was added to the diet. The patient was readmitted to the hospital and examination showed that there was a very low tolerance for protein. When the protein intake did not exceed 30 gm. the patient could tolerate upward of 50 gm. of carbohydrate and a total of 1,400 calories, whereas 45 gm. of protein and 30 gm. of carbohydrate caused small amounts of sugar to appear in the urine. The first test of muscular force was made after the patient had been under treatment for 390 days. She apparently was then in much better physical tone than when later observations were made. It is quite probable that this state of protein irritation existed for some time before its discovery. Before the 547th day of the treatment, the patient was eating from 65 to 90 gm. of protein daily, and probably was imperfectly utilizing it. After the 547th day of treatment, the protein intake was reduced to 30 gm., or less, with a general improvement in the condition of the patient, and a marked increase in the total calories which could

be safely ingested. Is it not probable that this apparent disturbance in protein metabolism and the low intake on which the patient was compelled to live had much to do with the material lessening of her muscular force?

TABLE 7.—DYNAMOMETER TESTS

Case 1709; man, aged 33. Table showing a comparison of the total calories in the diet, body weight, urine and lung air findings, with the measure of muscular force as determined by tests of grip strength.

Day of Treatment	Diet In Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO ₂ In Lung Air, Mm.
				Sugar, Gm.	NH ₃ , Gm.	
947	458	88½	R 14 - L 10	—	—	46.4
957	485	78¾	R 9 - L 7	—	—	40.4
964	1,410	81	R 9 - L 8	—	0.91	44.0
978	1,136	80	R 10 - L 6	1	—	39.8

COMMENT: Advanced diabetics who have a low food tolerance, who constantly exceed their metabolic limitations and who frequently show both glycosuria and ketonuria, usually become very weak and remain so. Case 1709 is a good illustration of this fact. The patient, a man, 33 years of age, began the treatment of his diabetes, June 29, 1914. In the beginning the danger of eating to the limit of tolerance was not realized, with the result that the patient was constantly fed up to or but little below that point, which was about 2,500 calories. The frequent recurrence of sugar in the urine was constantly associated with a lowering tolerance and increasing muscular weakness, so that in February, 1915, the patient was unable to eat more than 1,300 calories of food without glycosuria manifesting itself. During the summer of 1915 the patient for several weeks abandoned the diet, so that by August he had developed into a condition bordering on coma. He had a very marked acidosis, and it was with difficulty that he was made sugar and acid free. Aug. 25, 1916, his alveolar air was 21.4 mm. and he excreted in the twenty-four hours 2.57 gm. of ammonia. At this time he was very weak, indeed almost dead. Sept. 2, 1916, after being sugar and acid free for several days, and with a normal alveolar air (46.4 mm.), the first strength test was made. The patient was then 40 pounds under his usual weight and was on a diet of 458 calories. With his right hand he registered 14 kg., and 10 kg. with his left. During his stay in the hospital at this time it was evident that he could not safely tolerate more than 950 calories. He went home, however, and again began overeating to the point of having every few days a mild glycosuria and ketonuria, which he would correct by fasting. Under this plan of constant irritation he remained weak, as will be seen by the accompanying table. The first strength test was made after the patient had been under observation for 947 days, and the last test was made on the 978th day of observation. This table, unfortunately, only exhibits data of one brief hospital period, during which time he was under strict control. After two previous periods of hospital care, and following the one in which the above data were obtained, the patient relapsed into the habit of overeating, to the point of producing a mild glycosuria and ketonuria. Death finally resulted from exhaustion and coma. The career of this patient is typical, in so far as physical vigor is concerned, of the majority of patients who eat to the point of keeping their bodies in a state of metabolic exhaustion. The writer has notes on several similar cases, in all of which overeating led to a striking loss of muscular vigor, and, eventually, to exhaustion and death.

TABLE 8.—COMPARISON OF MUSCULAR FORCE AS DETERMINED BY STRENGTH OF GRIP WITH AGE, WEIGHT AND FOOD TOLERANCE IN A SERIES OF CASES

Case No.	Day of Treatment	Age	Weight, Net Pounds	Weight,* per Cent., Over (+) Under (—) Normal	Minimum Normal Caloric Needs of Patient	Caloric Tolerance of Patient	Strength Test,† Kg.
Males							
1877	14	57	120½	6 +	1,740	1,846	R 28 - L 22
1686	19	50	180	20 +	2,618	1,668	R 35 - L 32
1878	17	60	192¾	11 +	2,794	1,950	R 35 - L 30
1843	36	60	142½	14 —	2,070	1,727	R 30 - L 24
1845	26	27	182	24 —	1,920	2,039	R 46 - L 38
1866	16	67	130½	20 —	1,898	1,261	R 39 - L 31
1672	18	50	167	6 +	2,429	2,194	R 37 - L 32
1536	36	50	181¼	23 —	1,907	1,858	R 42 - L 37
1729	176	48	267	57 +	3,884	1,210	R 53 - L 43
1688	237	23	133	9 —	1,932	1,800	R 45 - L 38
1522	759	20	139	6 —	2,019	1,640	R 46 - L 34
1882	16	19	118	18 —	1,715	1,778	R 32 - L 28
1681	49	10	53½	21 —	777	618	R 6 - L 6
Females							
1787	115	52	184	4 —	1,949	960	R 26 - L 20
1890	18	32	88¾	36 —	1,290	1,141	R 20 - L 15
1816	26	47	113¼	13 —	1,648	1,775	R 22 - L 16
1799	22	68	160	3 —	2,326	1,075	R 12 - L 15
1545	67	39	75¼	45 —	1,094	736	R 16 - L 14
1532	208	29	108¾	17 —	1,580	1,105	R 18 - L 15
1739	214	62	203½	31 +	2,960	1,540	R 30 - L 20
1680	588	20	98	24 —	1,424	1,429	R 15 - L 11
1507	313	20	113	12 —	1,644	950	R 17 - L 18
1567	42	20	95	25 —	1,385	1,320	R 18 - L 16
1517	161	18	87	27 —	1,264	975	R 22 - L 17
1758	28	13	69½	20 —	1,011	1,210	R 10 - L 11
1718	28	14	68	29 —	989	843	R 11 - L 6

* Determined by dividing net weight by normal weight based on sex, age and height, according to the standards of the New York Life Insurance Company.

† The minimum normal pressure exerted by healthy men between 25 and 40 years of age, according to Hrdlicka, is right hand, 35 to 60 kg.; left hand, 20 to 35 kg.; women between 25 and 40 years of age, right hand, 25 to 38 kg.; left hand, 12 to 20 kg.

COMMENT: Diabetics as a rule are underweight. Allen has pointed out that patients have less difficulty in keeping sugar free when they are thin than when they are fat. In the foregoing tables the weights normal and actual are compared with the evidences of muscular force as shown by the strength of grip. It will be noted that although these patients, for the most part, were thin, some of them very thin, and were living on diets much below the normal minimum requirement (32 calories per kilo of body weight), they nearly all gave quite satisfactory responses to the test of muscular force.

SUMMARY AND CONCLUSION

1. This investigation supports the common clinical observation that diabetics, as a rule, are distinctly physically weaker than normal persons. Loss of body musculature may partly explain this, but it is probable that the lessened amount of food metabolized in these cases does not provide sufficient energy for the normal exercise requirements of the body. There appears to be a direct relationship between food tolerance and muscular vigor. As food tolerance increases, so does also muscular tone. Decline in food tolerance is accompanied by loss of physical vigor.

2. The continued use of a low diet for many months, even though it fall far short of the energy requirements of the body, provided it is within the physiologic limitations of the body to metabolize it, will cause an appreciable gain in muscular tone, although the amount of physical effort that such a person may be able to put forth may be considerably below the normal. This is in accord with clinical experience that nutrition within the tolerance of the patient gives the greatest comfort, strength and sense of well being and, as Joslin has pointed out, the greatest expectation of life.

3. These observations also show that while diabetics living on a diet below normal physiologic requirements possess a diminished muscular vigor, feeding them beyond their metabolic limitations causes not only a further reduction in their tolerance for food, but also an even greater loss of strength. This is contrary to the view commonly held by both physicians and laymen. There is no justification for the common notion that overfeeding causes even a temporary increase in comfort or body strength.

The general conclusion from this inquiry is that diabetics gain in physical vigor as they become and remain sugar free, while overfeeding causes a definite and often a serious loss of strength.

Attention is called to the use of the dynamometer as a simple and fairly trustworthy method of measuring muscular tone or physical vigor. For this purpose, it has a wide range of application in the study of metabolic and other diseases, and in my hands has yielded valuable information in the study of both diabetes and nephritis.

AURICULAR FLUTTER

A CONSIDERATION OF SOME PROBLEMS ARISING IN THE STUDY OF A CASE,
AND OF THE LITERATURE *

JAMES D. HEARD, M.D., AND ARTHUR E. STRAUSS, S.B., M.D.†
PITTSBURGH ST. LOUIS

Auricular flutter is that condition in which the auricles contract rhythmically and coordinately at a greatly accelerated rate, the lower limit of which has been arbitrarily placed by Lewis¹ at 200. The rate of the ventricles is usually slower than that of the auricles. This difference in rate is due to the fact that the ventricles fail to respond to every impulse originating in the auricles.

The term "auricular flutter" was first applied clinically by Jolly and Ritchie² in 1911; but the condition had been previously described as occurring in both humans³ and animals.⁴ Before the term was generally accepted, we find auricular flutter referred to as "jugular embryocardia," "auricular tachysystole," "auricular tachycardia," and "auricular tachyrhythmia."⁵ From the time that this disturbance in mechanism had been first recorded, until 1914, when Ritchie published his book, fifty-three cases, including those of Ritchie, had been reported. This fact, especially in view of the difficulty of diagnosis, indicates that the disorder is not uncommon. It has been reported as occurring in patients from 5 to 74 years of age, and in both sexes, though it predominates in the male. Of Ritchie's cases, 85 per cent. were males. Like other disturbances, flutter may be transient or permanent; it may last during a period of only a few seconds;⁶ but the tendency is toward a period of years. Its frequently transient nature, together with the absence, in some cases, of definite pathology, seems to indicate that it

* Submitted for publication April 5, 1917.

* From the Department of Medicine, University of Pittsburgh.

† R. B. Mellon Fellow in Internal Medicine.

1. Lewis, Thomas: Clinical Electrocardiography, Shaw & Co., London, 1913.

2. Jolly, W. A., and Ritchie, W. T.: Auricular Flutter and Fibrillation, Heart, 1910-1911, 2, 177.

3. Hertz, A. F., and Goodhart, G. W.: The Speed-Limit of the Human Heart, Quart. Jour. Med., 1908-1909, 2, 213. (Quoted by Ritchie. See Footnote 5.)

4. McWilliam, J. A.: Fibrillary Contraction of the Heart, Jour. Physiol., 1887, 8, 296. (Quoted by Levine, Footnote 13.)

5. Ritchie, W. T.: Auricular Flutter, W. Green & Son, Edinburgh and London, 1914.

6. Parkinson, J., and Mathias, H. H.: Tachycardia of Auricular Origin and Flutter with Phasic Variation in Auricular Rate and in Conduction, Heart, 1915, 6, 27.

may often be merely a local manifestation of toxemia. Therefore, even if no lesions be demonstrable in the auricle on postmortem examination, we need not deny the existence of flutter as a clinical entity. The general belief that there is a single point of stimulus production in the auricle has not been proved pathologically, for in no case has such a single focal lesion been recorded postmortem. We shall not discuss the etiology of flutter; we shall merely state that it has occurred during the course of such acute infections as pneumonia and diphtheria,⁷ in acute "endopericarditis,"⁸ during chloroform anesthesia,⁵ and in chronic alcoholism and arteriosclerosis.

During the study of the case to be presented, the several problems that interested us were: (1) a consideration of the contour of the auricular deflection, the P wave; (2) the auriculoventricular conduction time, A_s-V_s interval; (3) the auricular rate; (4) a study of blood pressure; (5) vagus action; (6) the mechanism of dissociation of auricles and ventricles in flutter and fibrillation; (7) the difficulties attending diagnosis; (8) therapy. The subjects will be discussed in sequence with the results of the investigation on our own case and a review of the literature. Any conclusions based on the study of a single case must be regarded as inferential rather than as proved.

HISTORY OF CASE

History.—W. B., man, white, single, aged 50 years; admitted to the medical service of Dr. H., St. Francis Hospital, Oct. 7, 1916; discharged Jan. 9, 1917.

Chief Complaints: Weakness associated with vertigo, dyspnea, and palpitation.

Present Illness.—For two weeks the patient had been drinking heavily and not feeling well. The morning of admission to the hospital, he had started to take a walk and had gone but a short distance when he became very dyspneic, weak, and dizzy; he also had marked palpitation, and had to sit down to rest. He started for his physician's office but had to rest frequently on the way. His physician brought him immediately to the hospital.

Past History.—Measles and mumps in childhood; said to have had "typhoid fever" at 18 and 28; alveolar abscess several years prior to admission. One year prior to admission patient fractured his right elbow; infection followed and he was in a hospital two months. He had never had chorea, rheumatic fever, or tonsillitis. There was no history of scarlatina. For ten years the patient had been subject to attacks of dyspnea, occurring two or three times a year, and lasting from a few days to several weeks. During such times dyspnea was intermittent, usually present on exertion, and accompanied by palpitation. Between attacks he had the normal capacity for work without dyspnea. During attacks of dyspnea the patient experienced a general weakness, felt faint and dizzy, "light-headed," but never lost consciousness. His physician asserted that at such times his pulse was rapid, 140 to 160. The attacks usually, but not always, followed drinking bouts. No edema was ever noticed.

7. Hume, W. E.: A Polygraphic Study of Four Cases of Diphtheria with a Pathologic Examination of Three Cases, *Heart*, 1913-1914, 5, 25.

8. Neuhoof, S.: Auricular Flutter Accompanying Acute Endopericarditis, *Med. Rec.*, New York, 1915, 88, 995.

The patient had never been cyanotic. Nycturia was present for twenty years; two or three times a night for the previous two years. No history of gonorrhea or syphilis.

Occupational History.—The patient had worked in a greenhouse for several years potting plants, and had done very little heavy work, such as lifting. Formerly he worked on a farm. Habits: Tea, 0-1 cup; coffee, 1-2 cups; tobacco, formerly used to excess, but recently in moderation; alcohol, excessive use since the age of 18; periodic drinking; sprees every few weeks; eight to ten whiskies, four to five beers daily.

Family History.—Negative.

Physical Examination.—Condition on admission: pulse rate 120, patient very dyspneic and complaining of extreme weakness. After a few hours in bed the pulse rate dropped to 60, and the subjective symptoms improved. The positive and salient findings were as follows: well developed and well nourished middle aged man; poor oral hygiene; jugular pulsation prominent, no abnormal waves recognizable; a few moist râles, which later disappeared, over both lower lobes.

Heart: Not enlarged to percussion; right border 4 cm., left border 12 cm. from midsternum; supracardiac dulness 6 cm. in width; apex palpable in fifth interspace with midclavicular line, 12 cm. to left of midsternum. The heart sounds were somewhat irregular as to force and rhythm, though many seemed of equal intensity and spacing. $A_2 > P_2$, but not accentuated. A harsh blowing murmur, apparently late systolic in time, was demonstrable at the apex and also in the axilla and over the lower sternum. The auricular contractions were not audible.

The radials were moderately sclerosed; volume of pulse was full; systolic blood pressure 132, diastolic 78; no pulse deficit. Liver dulness extended to 2 cm. below the costal margin; its edge was just palpable. No edema of extremities.

Laboratory Findings.—Blood picture practically normal; urine, negative on repeated examination; blood Wassermann, October 14, anticomplementary; November 4, positive with cholesterin antigen, negative with acetone—insoluble antigen; November 30, negative with both antigens.

Course and Treatment.—After a few hours in bed, the urgent symptoms disappeared and the pulse rate dropped one-half, as above noted. On several occasions it was observed that when the patient assumed an erect posture the pulse rate was exactly doubled. No medication was given until November 1, when the patient was placed on digitalis tincture, 20 minims three times a day. Digitalis was omitted for two doses, November 6 and 7 (*vide infra*), and was then continued as before until November 17, when auricular fibrillation was established and the drug omitted. November 20, the patient had a slight attack of acute follicular tonsillitis (mixed infection), lasting three days, with rise in temperature and pulse and general malaise. The patient was confined to bed during digitalis administration and afterward until December 13. He was then permitted to get up, effort being gradually increased. There were no cardiovascular symptoms after the first few days in the hospital. On discharge, Jan. 9, 1917, the auricles were still fibrillating. The size of the heart at this time was apparently the same as on admission.

THE P DEFLECTION⁹

The contour of the auricular deflection has been the subject of controversy since the first case of flutter was studied by the electrocardio-

9. Unless otherwise stated we shall refer to the P waves in Lead II (right arm—left leg) in this discussion.

graph. Thus it has been described by various observers as upright,¹⁰ invert,¹¹ or diphasic, with the primary deflection upward,¹² or downward.¹³

We believe that the auricular deflection in our case is diphasic, and that it begins with a downstroke. The auricular deflection shows an iso-electric phase in the middle of the downstroke (Fig. 1), a phase which we believe corresponds to the diastole of the auricle and separates one auricular complex from the next. This belief is based on the following reasoning: (1) In certain electrocardiograms in our series the P of Lead I is diphasic, primarily downward (Fig. 2); (2) an iso-electric phase within the limits of auricular systole is of extreme rarity. Thus, in a study of over 300 cases in our own series, of which twenty-one showed diphasism of the P wave, such a phase does not occur in a single instance. Furthermore, in only one case in

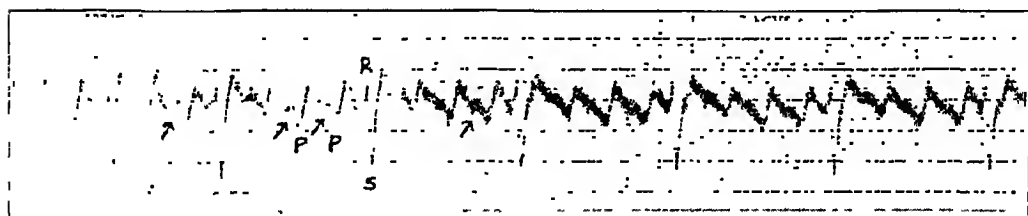


Fig. 1.—(No. 2, Lead II). Electrocardiogram showing the iso-electric phase which we believe represents auricular diastole. The P wave is diphasic, primarily downward.

The ordinates in all electrocardiograms shown represent 10^{-4} volt, the heavy and fine abscissae represent time intervals of $\frac{1}{6}$ and $\frac{1}{25}$ second, respectively. All figures except Figures 12, 13, and 14 are from the case described in the body of paper.

the literature have we seen such a curve, that shown by Ritchie⁵ in a case of complete block following flutter, in which there is an iso-electric line in the middle of the P wave which is diphasic but primarily upward (see Ritchie's Fig. 34); (3) Lewis¹⁰ asserts that, "the normal length of P is decidedly under 0.20 second, and if the auricular rate is fast,

10. Lewis, T.: Observations on a Curious and not Uncommon Form of Extreme Acceleration of the Auricle, "Auricular Flutter," *Heart*, 1912, **4**, 171. See also Ritchie, Footnote 5.

11. Parkinson, J., and Mathias, H. H.: Tachycardia of Auricular Origin and Flutter with Phasic Variation in Auricular Rate and in Conduction, *Heart*, 1915, **6**, 27. Rihl, J.: Hochgradige Vorhofftachysystolen mit Ueberleitungstörungen und electiver Vaguswirkung, *Ztschr. f. exper. Path. u. Therap.*, 1911, **9**, 277 (Quoted by Lewis, Footnote 10). Lewis, T.: Observations on Disorders of the Heart's Action, *Heart*, 1912, **3**, 279.

12. Cohn, A. E.: Auricular Tachycardia with a Consideration of Certain Differences Between the Two Vagi, *Jour. Exper. Med.*, 1912, **15**, 49. See also Footnote 5.

13. Levine, S., and Frothingham, C., Jr.: A Study of a Case of Auricular Flutter, *THE ARCHIVES INT. MED.*, 1915, **16**, 818.

P is shorter than this." In our case, the duration of the auricular deflection, if the iso-electric phase be excluded, would be about 0.18 second. This is more nearly normal than 0.28 second, which would be the duration with the iso-electric line included in auricular systole. It is, in fact, so nearly normal that we do not need the added factor of a development of electric potential during auricular diastole which Lewis finds necessary to explain his theory of the contour of P. This author illustrates his point by Figure 31 of his article,¹⁰ in which he gives 0.22 second as the duration of P. The figure shows the iso-electric line, and if this is excluded as being a manifestation of diastole, the P wave would measure between 0.11 and 0.12 second, as we should expect. Should our conception of P be generally applicable, Lewis'¹⁰ rule, that the length of the auricular cycle in flutter is inversely and exactly proportional to the rate, would be overthrown; (4) Lewis¹⁰ says that if the auricular rate is over 260 a minute, the P waves will be contiguous. In our case, in which the iso-electric line is so often

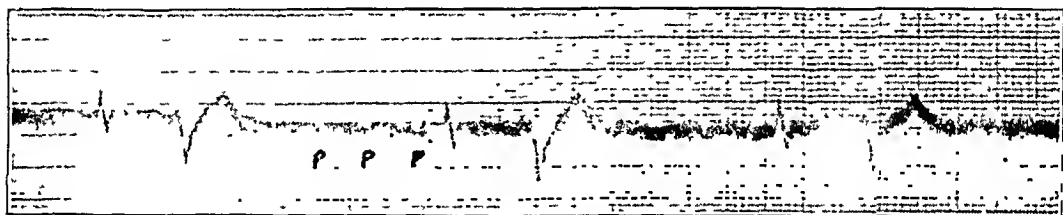


Fig. 2.—(No. 28, Lead I). Electrocardiogram showing the diphasic character of the P wave in Lead I. P is primarily downward.

prominent, the rate varies between 230 and 255, thus falling below that thought necessary for contiguity, and leaving a period for the manifestation of diastole, namely, the iso-electric phase. This latter reasoning, however, cannot be universally applicable, since such an iso-electric phase has occurred in the reported cases with rates as high as 281 (Ritchie,⁵ Case 2, Figs. 47 and 81). In Jolly and Ritchie's original report on flutter,² the iso-electric phase is very definite with an auricular rate of 272 (their Fig. 20). Two other cases of flutter in our series, however, fail to show the iso-electric line. From the foregoing statements it is evident that there is no constant shape of P in flutter. Even all of our curves in this case do not show a definite iso-electric line.

In agreement with the general impression, we find no change in the shape of the P wave, either as a result of vagus pressure or of digitalis administration in our flutter case, although in cases in which the pacemaker is believed to be at the normal site, vagus stimulation reduces the height of P both in man¹⁴ and in dogs.¹⁵ Whether or

14. Robinson, G. Canby, and Draper, G.: Studies with the Electrocardiograph on the Action of the Vagus Nerve on Human Hearts. II. In Children with Chronic Valve Disease, *Jour. Exper. Med.*, 1912, **15**, 14.

15. Goddard, C. H.: Changes in the P Wave in Human Electrocardiograms, *THE ARCHIVES INT. MED.*, 1915, **16**, 633.

not the stimulus production in flutter may originate at the normal pacemaker, is still uncertain, but the mass of evidence is in favor of an ectopic origin.

A_s-V_s INTERVAL

The determination of the conduction time in flutter has been of interest because of the great rapidity of auricular rate, which makes it difficult to determine to which auricular stimulus the succeeding ventricular complex corresponds. After measuring the P-R intervals in many curves, Lewis decided that the ventricle responds not to the auricular beat immediately preceding, but to the second one before it. This has been our guide in the measurement of the A_s-V_s interval, and on these measurements we base our conclusions.

We found a great variation in the length of this interval, which we believe to be due, not to the occasional indistinctness of the beginning of the P waves, but to other factors little understood at present. The

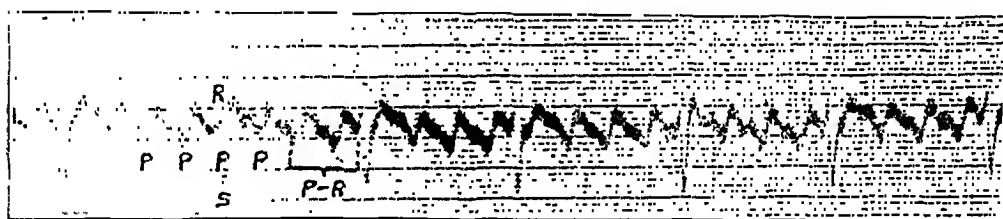


Fig. 3.—(No. 1, Lead II). Electrocardiogram taken Oct. 12, 1916, before administration of digitalis. The P-R intervals are 0.48, 0.44, 0.41, 0.48, 0.42, 0.42 second, reading from left to right. Note absence of relationship between P-R intervals and degree of block or length of preceding pauses (R-R intervals). The P-R intervals are measured from the beginning of the downstroke of P (following the iso-electric phase) to the beginning of the R wave.

same differences are seen if we consider the P wave as diphasic, upright, or invert, and take corresponding points for our measurements. Thus, in our first plate (Fig. 3), we find a variation in the P-R interval of 0.07 second, our measurements for one lead being 0.48; 0.44; 0.41; 0.48; 0.42; 0.42 second. Lewis,¹⁰ Fulton,¹⁰ and others state that the A_s-V_s interval varies with different degrees of block, there being a shorter conduction time following a long pause, and a longer P-R interval following a short pause. That the variation noted in our case is not due to this factor is made clear by measuring the preceding pauses (R-R intervals). Likewise, in our other curves of the case, we find no constant relationship between the degree of block and the conduction time.

16. Fulton, F. T.: Auricular Flutter with a Report of Two Cases, *THE ARCHIVES INT. MED.*, 1913, **12**, 475.

Cohn and Lewis,¹⁷ in experiments on dogs, in which the auricles are kept at a constant rate by electrical shocks, find that stimulation of the left vagus prolongs conduction time more than does stimulation of the right. In general we find, where the same degree of block is produced by right and left vagus stimulation, that the P-R interval is slightly longer with left vagus stimulation than with right, but that the difference is no greater than that occurring spontaneously, and our series is too small to allow any definite conclusions to be drawn. We can only say that the results are suggestive of confirmation of the experimental work done in animals.

Digitalis is supposed to exert its beneficial action partly by causing prolongation of the P-R interval, and by increasing the degree of block. Later in this paper we shall discuss the increase in block due to digitalis. We are at present interested in its effect on the conduction time. In Plate 25, Lead III (Fig. 4), taken after 460 minims of tincture of digitalis had been given, if we measure the P-S interval (which

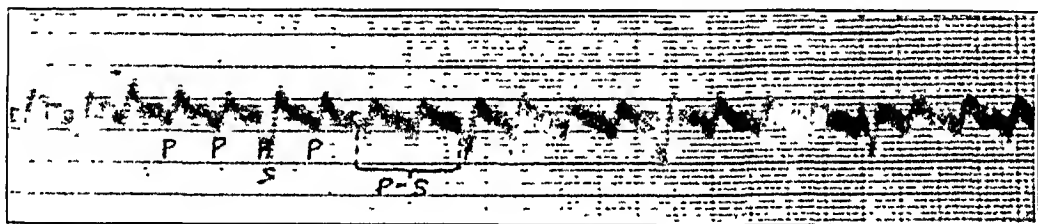


Fig. 4.—(No. 25, Lead III). Electrocardiogram taken after administration of 460 minims of tincture of digitalis over a period of nine days, showing prolongation of the conduction time (P-S interval). The iso-electric phase of the auricular deflection is well shown.

corresponds to the P-R interval of Lead II) from the P immediately preceding the ventricular complex, we find that it varies from 0 to 0.08 second; or, if we take the case where the S wave begins on the iso-electric line, the interval in that instance would be 0.28 second. Measuring from the next preceding P, we find a variation from 0.32 to 0.34 second, or, in the one case, 0.54 second. In 4-1 block before digitalis was begun the P-R interval was 0.41 to 0.48 second. It is a well-known fact that during normal mechanism digitalis may prolong the conduction time, and it would be unusual for the drug to act in the opposite manner in flutter. However, if the third preceding P wave is taken as the stimulus that causes the ventricle to contract, we get a measured A_s - V_s interval of 0.54 to 0.60 second, which agrees with the prolongation seen in normal mechanism as a result of digitalis administration. This is, with little doubt, the conduction time in this case.

17. Cohn, A. E., and Lewis, T.: Predominant Influence of Left Vagus Nerve on Conduction Between Auricle and Ventricle in Dogs, *Jour. Exper. Med.*, 1913, **18**, 739.

AURICULAR RATE

The rate of the auricle in the individual case of flutter usually tends to remain the same under varying conditions and at different times, unaffected by postural changes or nervous influences.¹⁰ However, we believe that too much stress has been laid on this aspect of flutter. Indeed, many instances are cited in which a distinct change in rate has been noted. Lewis in his monograph gives several examples; White¹⁸ notes a difference of 44 in the rate at different times; Parkinson and Mathias,⁶ in their unique case, note a gradual change from 240 to 200 during the flutter period. Our case shows a variation from 230 to 255. The changes are apparently spontaneous, however, not occurring in definite relation to those influences that are normally supposed to affect the heart rate, although the slight slowing produced by deep breathing observed by Levine and Frothingham¹³ was attributed by them to vagus effect, and the change in auricular rate in the case of Parkinson and Mathias was also believed to be due to nervous influences.

In our case, the auricular rate became somewhat slower during full digitalization. Whether this result was an effect of the digitalis, or merely coincidental, cannot be said with certainty.

The rate of stimulus production in fibrillation is increased over that in flutter, and as a result the ventricles usually beat more slowly when the change from flutter to fibrillation occurs. This effect may be due partly to the fact, experimentally determined, that acceleration of the auricles in the presence of slight grades of block tends to a reduction of the ventricular rate;¹⁰ but it may be due also in part to the fact that many of the auricular stimuli in fibrillation have not the minimum threshold value necessary either for conduction through the junctional tissues or for excitation of response of the ventricular musculature itself.

BLOOD PRESSURE

Very little careful study has been made of the correlation of blood pressure during flutter and fibrillation in a given case. Ritchie⁵ says that in flutter a systolic blood pressure as high as 260 to 275 mm. of mercury has been recorded, and he believes that the age incidence suggests some relationship between arteriosclerosis and flutter. Levine and Frothingham¹³ made a study of the blood pressure in their case and noted a decrease in pulse pressure during the normal period as compared with that during the period of flutter.

We began our investigations of blood pressure during the period of flutter and hoped to be able to compare the three phases of flutter, fibrillation, and normal mechanism. At the time of writing, however

18. White, P. D.: A Study of Auriculoventricular Rhythm Following Auricular Flutter, *THE ARCHIVES INT. MED.*, 1915, **16**, 517.

(March, 1917), the case is still in fibrillation. We can, therefore, present our findings for only the first two phases. All the blood pressure readings were taken by one of us (S), who assumes individual responsibility for this portion of the article. The pressures were all taken under approximately the same conditions: with the patient in bed continually until December 13; from the 13th to the 19th, inclusive, with the patient lying in bed, although he was up part of each day; all thereafter, with the patient sitting up and out of bed during the whole day.

The "average systolic" blood pressure was taken according to the method of James and Hart.¹⁹

The force of the pulse during flutter was nearly constant over long periods of time; so it was not thought necessary to take an average systolic reading, although that course might have been advisable because of an occasional relative pulse deficit. During the period of fibrillation it was noted, with some surprise, that the point at which the first systolic sound was heard over the brachial artery on lowering the pressure in the cuff, after the pulse had been obliterated, varied within such narrow limits that we felt justified in using that point as an index to the systolic reading. The same observation was made regarding the point marking the change from the loud, clear sound of the third phase to the muffled, low sound of the fourth phase, which was called the diastolic pressure.²⁰ To obtain such results, however, the pressure changes in the cuff must be made slowly when approaching these points.

The accompanying table (Table 1) will show our readings during the study, the summary of which follows (Table 2).

Despite the great daily variation in pressure, there was nothing in the patient's general condition to indicate such change. There was a definite fall in pulse pressure during the change from flutter to fibrillation, and if we take the "average systolic" as indicative of the true pressure in fibrillation, the fall in systolic pressure was very marked. It would seem that with such a fall there would be some change in the condition of the patient; yet none was noticeable and the patient was aware of no change.

In this case, the daily variation of the "average systolic" blood pressure was almost as great as that of the systolic pressure taken in the usual way. This observation threw some doubt on the value of the

19. James, W. B., and Hart, T. S.: *Auricular Fibrillation: Clinical Observations on Pulse Deficit, Digitalis, and Blood Pressure*, *Am. Jour. Med. Sc.*, 1914, **147**, 63.

20. Warfield, L. M.: *Studies in Auscultatory Blood Pressure Phenomena. The Clinical Determination of Diastolic Pressure*, *Jour. Am. Med. Assn.*, 1913, **61**, 1254.

TABLE 1.—BLOOD PRESSURE

Mechanism*	Date	Systolic	Diastolic	Pulse Pressure	Average Systolic
Flutter.....	10/12/16	132-128	78-68	54-60	...
Flutter.....	10/20/16	132	80	52	...
Flutter.....	10/23/16	128	76	52	...
Flutter.....	11/ 4/16	110	65	45	...
Flutter.....	11/ 6/16	118	65	53	...
Flutter.....	11/ 9/16	135	75	70	...
Flutter.....	11/10/16	115	70	45	...
Flutter.....	11/14/16	138	60	78	...
Fibrillation.....	11/17/16	110†	60‡	50	70
Fibrillation.....	11/18/16	107-105	70-60	37-45	93
Fibrillation.....	11/19/16	150-140	80-65	70-75	105
Fibrillation.....	11/20/16	83
Fibrillation.....	11/22/16	105	60	45	98
Fibrillation.....	11/23/16	120-115	75	45-40	111
Fibrillation.....	11/25/16	118-110	75-65	43-45	108
Fibrillation.....	11/26/16	110	60	50	97
Fibrillation.....	11/27/16	112	62	50	105
Fibrillation.....	11/29/16	112	74	38	102
Fibrillation.....	11/30/16	115-112	70-65	45-47	90
Fibrillation.....	12/ 2/16	112-110	62-60	50-50	96
Fibrillation.....	12/ 5/16	118	74	44	110
Fibrillation.....	12/ 8/16	110	65	45	91
Fibrillation.....	12/11/16	112	75	37	100
Fibrillation.....	12/13/16	130	80	50	109
Fibrillation.....	12/15/16	110	80	30	98
Fibrillation.....	12/19/16§	114	74	40	98
Fibrillation.....	12/27/16	80- 75	50-45	30-30	84
Fibrillation.....	12/29/16	90	60	30	85
Fibrillation.....	1/ 2/17	99
Fibrillation.....	1/ 6/17	107	60	47	107
Fibrillation.....	1/ 9/17	120	72	48	111
Fibrillation.....	1/12/17	128	80	48	119

TABLE 2.—SUMMARY OF READINGS PRESENTED IN TABLE 1

Mechanism and Posture of Patient	Systolic		Diastolic		Pulse Pressure		"Avg. Syst."
	Min.	Max.	Min.	Max.	Min.	Max.	
Flutter—lying in bed.....	110	138	60	80	48	78
Average	126		72		56	
Fibrillation — patient lying in bed	105	150	60	80	37	75	70-111
Average	115		67		47		98
Patient up part of day; pressure taken lying in bed..	110	130	74	80	30	50	98-109
Average	118		78		40		101
Patient up all day; pressure taken with patient sitting up	75	128	45	80	30	48	84-119
Average	100		61		39		101
Fibrillation — All above postures combined	75	150	45	80	30	75	70-119
Average	111		68		42		100

* Mechanism determined by electrocardiogram.

† During fibrillation, first sound heard with stethoscope over brachial called systolic.

‡ During fibrillation, the change from the loud, clear sound of the third phase to the muffled, low sound of the fourth phase called diastolic.

§ Pressure taken with patient in bed up to this date; thereafter with patient up.

"average systolic" reading, which though not difficult, is nevertheless time-consuming and a tax on the patience of physician and patient alike.

There was a marked constancy in the diastolic pressure during both flutter and fibrillation, with no change noted in the transition from one to the other.

While no conclusions can be drawn from the study of this single case, similar observations on other cases would be of value.

VAGUS EFFECT

As contrasted with the studies of blood pressure, observations on the effects of vagus stimulation in flutter and its allied conditions are many and they rest both on experimental work and on clinical observation. Cohn²¹ gives an excellent chronological summary of the important work on the vagus. Czermak, in 1865, first described the method of stimulation of the vagus by pressure over the carotid artery in the neck; we believe this to be the method of choice in man. More recently, 1908, Aschner²² described the oculo-cardiac reflex by which vagus effects may be obtained by pressure on the eyeball. Both methods were used in our case. In a series of tests during both flutter and fibrillation we obtained better results by pressure over the carotid than on the eyeball, although several investigators²³ have found the latter method more reliable. Levine²² says that pressure over the eyeball does not cause pain; but in the case of no patient have we found this statement verified.

During flutter we could obtain ventricular standstill or definite slowing by pressure over right or left carotid or on either eyeball; the most pronounced effect was obtained by the Czermak method, and on the right side more than on the left (Figs. 5 and 6). An interesting exception occurred when, on one occasion, by left vagus pressure we obtained a ventricular standstill of 9.2 seconds. During this time the patient momentarily lost consciousness and showed the beginning of tonic and clonic movements of arm, thus causing the writing pen of the radial tambour to leave the tracing paper (Fig. 7). The patient, when asked to describe his feelings afterward, said that he "felt light-headed and dozed off." We believe that by vagus pressure in this instance we produced an artificial Stokes-Adams syndrome. There-

21. Cohn, A. E.: Difference in Effects of Stimulation of the Two Vagi on Rate and Conduction in the Dog's Heart, *Jour. Exper. Med.*, 1912, **16**, 732. See also Footnote 12.

22. See Levine, S.: The Ocular Reflex, an Electrocardiographic Study with Special Reference to the Differences Between R. and L. Vagal and Ocular Pressures in Tabetics and Non-tabetics, *THE ARCHIVES INT. MED.*, 1915, **15**, 758.

23. Ferralis, G. V., and Pezzi, C.: Reflexe oculo-cardiaque et extrasystoles, *Arch. d. mal. du cœur*, Paris, January, 1916, **9**, 1; abstr. *Jour. Am. Med. Assn.*, 1916, **66**, 924. See also Footnote 13.

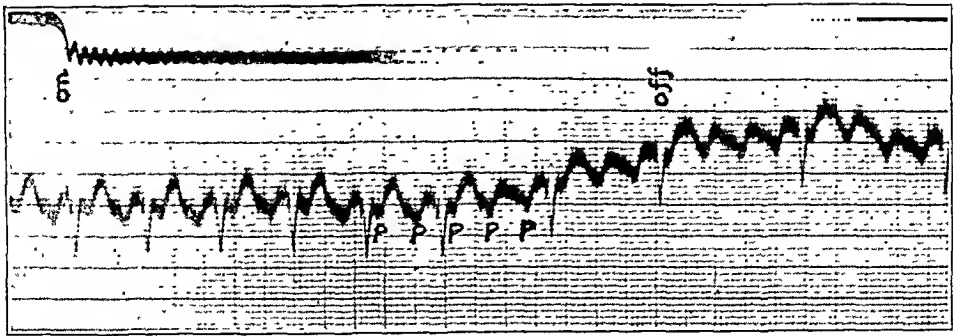


Fig. 5.—(No. 12, Lead II). Left carotid pressure during flutter. An electrocardiogram showing increase in degree of block due to vagus stimulation. Note latent period before effects of pressure become evident and residual action after pressure is released. Upper line is signal showing duration of pressure.

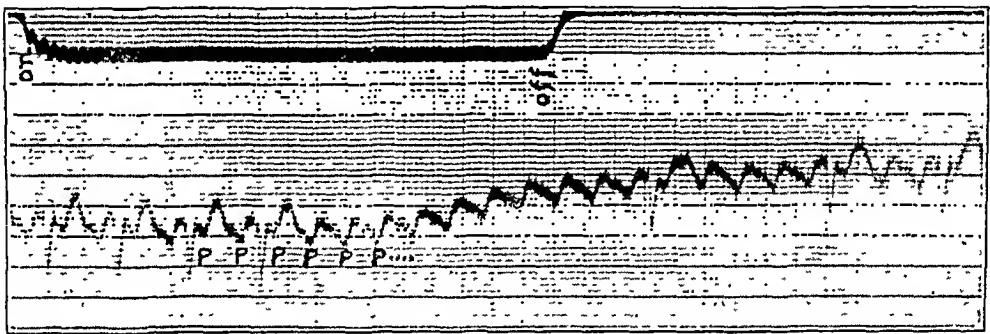


Fig. 6.—(No. 13, Lead II). Right carotid pressure during flutter. Electrocardiogram showing 11-1 block as a result of right vagus stimulation. Before pressure there was a regular 2-1 block. During pressure the auricles continue to beat as before. Latent period and residual effect are evident.

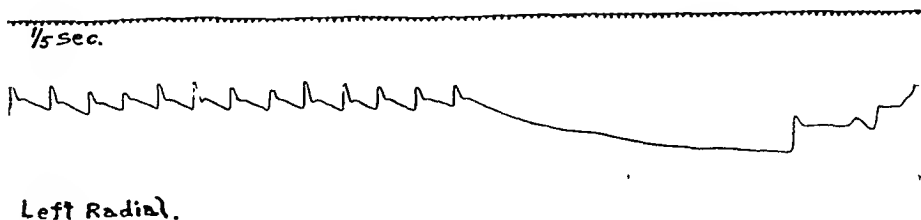


Fig. 7.—Tracing from left radial artery showing effect of pressure over left carotid. During the period of ventricular asystole, which lasted more than nine seconds, the patient experienced an artificial Stokes-Adams syndrome. Each division of time-marker represents $\frac{1}{5}$ second. Tracing made before administration of digitalis. (Fig. 7 retraced.)

after, because of danger to the patient, we never produced sufficient pressure to cause such a prolonged period of asystole. With much shorter periods of asystole, however, the patient said he felt "light-headed" as during the attacks of dyspnea and weakness described in the case history.

There was always a latent period between the onset of pressure and the first effect, but the time of this could not be accurately determined because of the uncertainty of the method employed, the onset of stimulation not being synchronous with onset of pressure on the neck. Robinson and Draper²⁴ mention this uncertainty of time of onset as

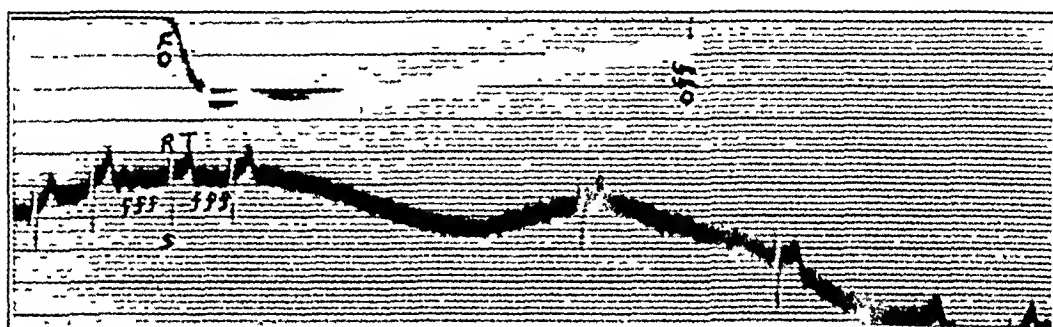


Fig. 8.—(No. 59, Lead II). Right carotid pressure during auricular fibrillation. The longest period of ventricular asystole (R-R interval) was 4.1 seconds. The plate was moving more slowly than in preceding figures. The abscissae, although indistinct in the prints, are clearly shown in the original photographic plates. The upper line is a signal showing duration of pressure.

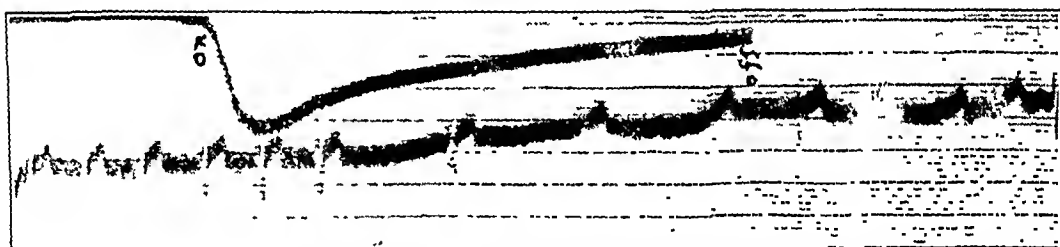


Fig. 9.—(No. 60, Lead II). Left carotid pressure during auricular fibrillation. Note legend of Figure 5.

one of the disadvantages of this method of vagus stimulation and assert that others are the uncertainty of result, the impossibility of measuring the strength and duration of the stimulus, and the danger to the patient. In their experiments they observed no ill effects, only one case showing transient vertigo, but our observation of loss of consciousness as a result of long asystole warned us that the method is not without danger. After pressure was released, the effects of vagus stimulation continued for some time.

24. Robinson, G. Canby, and Draper, G.: Studies with Electrocardiograph on the Action of the Vagus on Human Hearts. I. Effect of Mechanical Stimulation of the Vagus Nerve, *Jour. Exper. Med.*, 1911, **14**, 217.

During stimulation by carotid pressure, there was an occasional tendency toward ectopic beat formation such as noted in eyeball pressure;²⁵ otherwise no change occurred in the ventricular complex of the electrocardiogram, and the auricles were entirely unaffected as to rate or form, a fact already noted by all investigators who have studied this aspect of the question. This is further evidence of the ectopic origin of stimulus production in flutter, for in normal hearts in both man¹⁴ and animal¹⁷ the auricles are under vagus control—the right vagus with greater control over the site of stimulus production, the left with preponderant action on the conduction tissues.²⁶

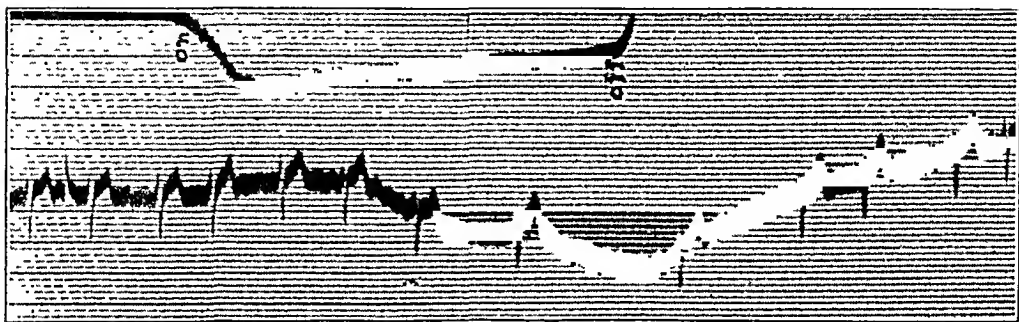


Fig. 10.—(No. 61, Lead II). Right ocular pressure during auricular fibrillation. Note legend of Figure 5.

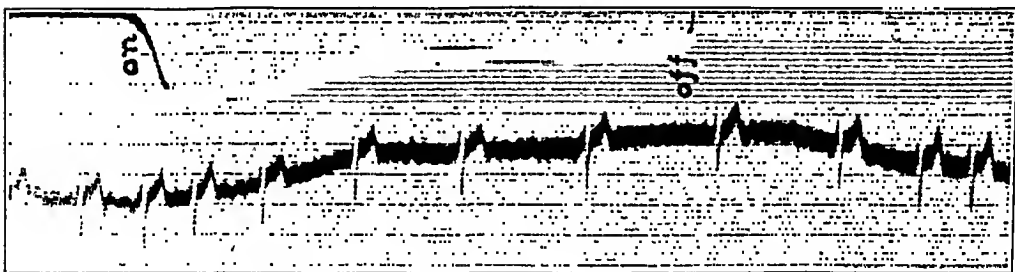


Fig. 11.—(No. 61, Lead II). Left ocular pressure during auricular fibrillation. Note legend of Figure 5.

This effect, though the rule, has its exceptions, noted both clinically and in experimental animals; thus Cohn,²¹ in two out of fifty-four experiments, finds the opposite action from that expected. Robinson and Draper¹⁴ find right and left vagi acting alike in one case and contrary to rule in another. White,¹⁸ in his flutter case, finds the right vagus more effective in increasing block than the left, a result similar

25. Ferralis, G. V., and Pezzi, C.: *Reflesso oculocardiaco e extrasistoli*, Policlinico, Rome, 1916, **23**, Med. Sect., p. 129; *Abstr. Jour. Am. Med. Assn.*, 1916, **66**, 2129.

26. See Footnotes 12, 14, 17, 21, and 24, and Cohn, A. E.: *Effect of Morphin on the Mechanism of the Dog's Heart after Removal of One Vagus Nerve*, *Jour. Exper. Med.*, 1913, **18**, 715.

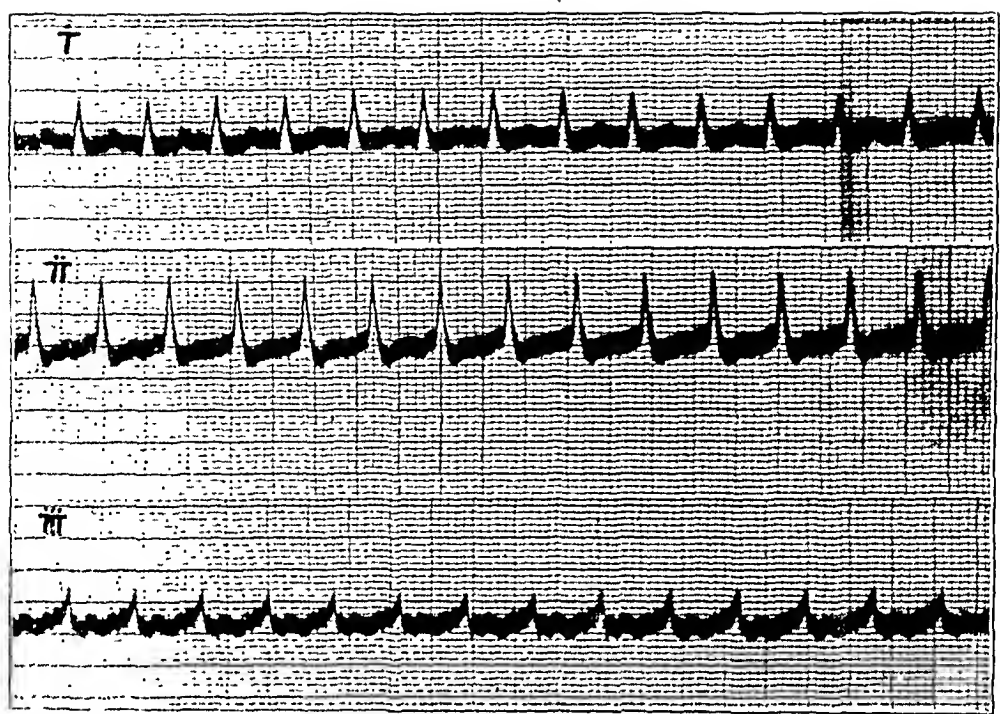


Fig. 12.—(A 321, No. 2, Leads I, II, III). Electrocardiogram taken during period of regular 2-1 block in a case of auricular flutter showing difficulties of diagnosis sometimes experienced despite graphic methods. Auricular rate 375; ventricular rate 187.5. Same case as Figures 13 and 14.

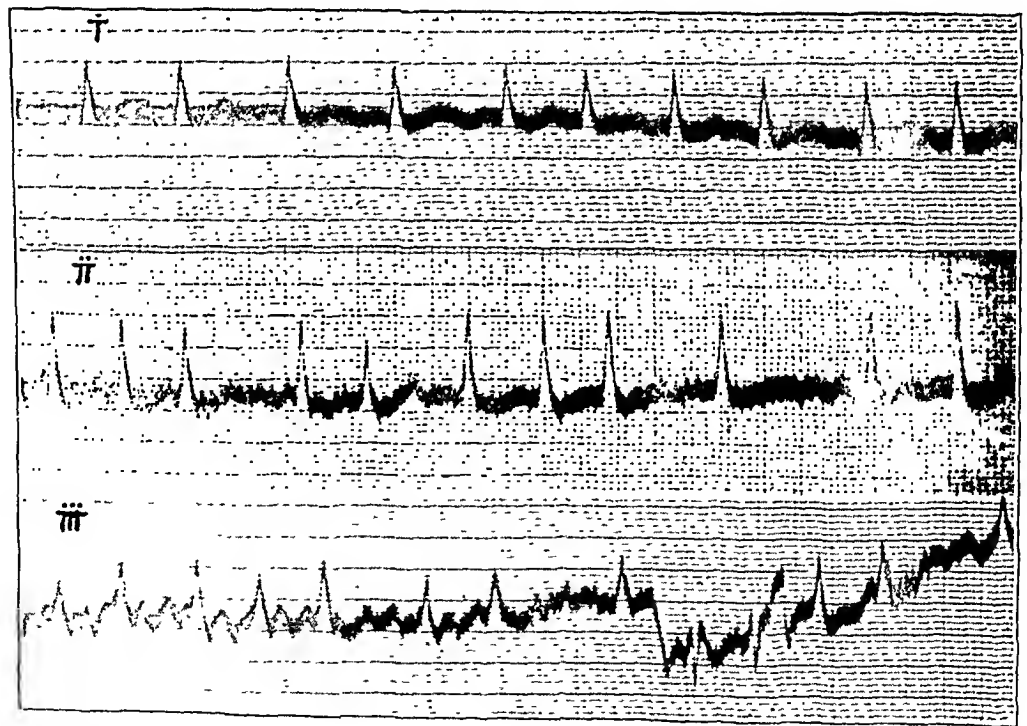


Fig. 13.—(A 321, No. 6, Leads I, II, and III). Electrocardiogram taken during period of irregular ventricular response in auricular flutter, showing close resemblance to auricular fibrillation. The latter part of Lead III is distorted by body movements of the patient. Same case as Figures 12 and 14.

to ours. Lewis¹⁰ says that both vagi act alike, suggesting "control of the junctional tissues in man by both vagi and failing to substantiate the view of preponderance of one over the other." Ritchie⁵ likewise says in reference to the selective action of the two vagi in animals that "it is doubtful whether this holds good with the human heart." Robinson and Draper,¹⁴ however, after a series of experiments on man arrive at the conclusion that "in healthy as well as in diseased hearts the control of rate of the heart beat predominates in the right vagus and the control of stimulus conduction preponderates in the left vagus, not because of any specific activity in the nerves themselves, but, as Dr. A. E. Cohn has suggested to us, on account of a possible difference in the anatomic distribution of the two nerves." This conclusion seems to be borne out by a clinical study since made,²⁷ although it is only a quantitative and not a qualitative difference, and cannot be taken as an absolute rule, because of frequent exceptions.

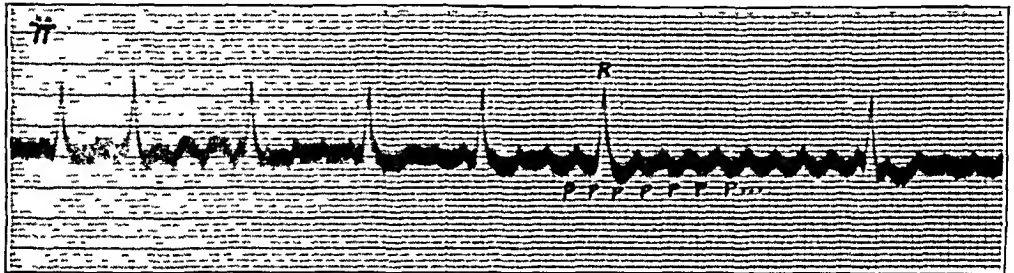


Fig. 14.—(A 321, No. 8, Lead II). Pressure over left carotid. Electrocardiogram of same case as that pictured in Figures 12 and 13, showing the value of vagus pressure as an aid to diagnosis in auricular flutter. Pressure was exerted throughout the entire portion shown. Auricular rate 375. During the long diastolic pauses the P waves are prominent. Picture taken immediately after that shown in Figure 13.

After the change in mechanism in our case, we repeated the experiments with the auricles in fibrillation, with approximately the same result as seen in flutter (Figs. 8, 9, 10 and 11).

Robinson and Draper,²⁴ working on normal hearts in man, noted that with R vagus stimulation the maximum pause initiated the onset of slowing, while with L vagus stimulation the maximum pause was delayed. In neither flutter nor fibrillation did we find any constancy in such effects, either by eyeball or carotid pressure.

The value of vagus pressure as a diagnostic aid in the interpretation of questionable electrocardiograms was brought forcibly to our attention in another patient with flutter who entered the hospital while this paper was being written. In this case (as yet unpublished), the auricular rate was 375, and the ventricular 187.5. From the electrocardio-

27. Cohn, A. E., and Fraser, F. R.: Paroxysmal Tachycardia and the Effect of Stimulation of the Vagus Nerves by Pressure, *Heart*, 1913, 5, 93.

grams taken during regular 2-1 and irregular degrees of block, a positive diagnosis of flutter could not be made. However, with pressure over the carotid, the block was increased; the auricles continued to beat as before while the ventricles were slowed, and the electrocardiogram then showed the typical curve of flutter, making diagnosis easy (Figs. 12, 13 and 14).

THE MECHANISM OF AURICULO-VENTRICULAR DISSOCIATION IN FLUTTER AND FIBRILLATION

Mention has already been made of the fact that in auricular flutter the ventricles seldom keep pace with the auricles, there being usually some degree of dissociation between them. The generally accepted view of this dissociation is that the impulses arising in the auricle are "blocked" in the auriculo-ventricular conduction tissue, and thus fail to reach the ventricles. If there is an actual blocking of the impulses in the junctional tissues, the question arises why, in the return to normal mechanism, there is frequently no conduction defect (prolongation of A_s-V_s interval)? If we deny the presence of auriculo-ventricular block, we must in some way account for the dissociation. Is it due to fatigue of the junctional tissues or the ventricular muscles so that they will not respond to every stimulus? This causation seems improbable, because we often get more rapid contraction than is shown in flutter with 2-1 and 4-1 block without any evidence of fatigue in either conduction tissue or musculature. Lewis¹⁰ believes that there is a primary deficiency of conduction in cases exhibiting block, because the junctional tissues have been shown capable of conducting impulses at the rate of 290 to 300 per minute, while in block, conduction is much less frequent. The longer A_s-V_s interval following a short pause and the shorter conduction time after a long pause, noted by other observers, is evidence in favor of the defect being in the junctional tissues rather than elsewhere, but we believe a factor that has been too little considered is the refractory period of muscle.

Foster,²⁸ as early as 1872, made the observation that weak, interrupted currents inhibit the heart in diastole. Since that time physiologists have repeatedly confirmed this observation. Carlson²⁹ asserts that it is not even necessary to have very rapid stimulation to produce this effect; that two or three shocks per second induce diastolic standstill in the hearts of some animals. We know, then, that heart muscle shows a prolongation of refractory period under frequently repeated

28. Foster: Pflüger's Arch. f. ges. Physiol., 1872, 5, 191 (Quoted by Carlson, Footnote 29).

29. Carlson, A. J.: The Nature of the Inhibition of the Heart on Direct Stimulation with a Tetanizing Current, Ztschr. f. allg. Physiol., 1907, 6, Parts 3 and 4.

stimulation. It should make no difference whether the stimulus is artificial, like that produced by repeated induction shocks applied to ventricle, or whether it comes through the usual channels from the auricle. In flutter the auricles are beating more than 200 per minute, while in fibrillation the rate of stimulus production is even more rapid, so that if these rapidly repeated impulses reach the ventricles they may cause a prolongation of the refractory period of the ventricular musculature, and in that manner produce dissociation of auricles and ventricles, dissociation usually attributed to auriculo-ventricular "block."

DIAGNOSIS

To quote from Ritchie:⁵

Whenever a patient complains of sudden attacks of palpitation and dyspnea, with or without precordial pain, syncope, or other symptoms, and the pulse rate during the attack attains or exceeds 130 to 140 per minute, auricular flutter should be suspected. If the pulse during the attack is absolutely rhythmic, the condition is probably due to flutter. Moreover, if the attack of rhythmic tachycardia comes on suddenly and either ends abruptly, or the rate of the rhythmic pulse beats falls one-half, while the patient is taking digitalis, the auricles are almost certainly in flutter.

This statement does not cover the entire field, since, with the exception of the implied digitalis action in flutter, it would apply equally well to paroxysmal tachycardia — a disturbance of mechanism, which is not fully mentioned by Ritchie in the discussion of diagnosis, inasmuch as he only mentions that tachycardia arising in the junctional tissues, and not that arising in either auricle or ventricle. It is worthy of note that Lewis¹⁰ states that one should suspect flutter if sinus arrhythmia fails to appear with forced respiration, or if, on the other hand, slight exercise results in a sudden doubling of rate. While recognizing the importance of clinical observation, however, one must, nevertheless, admit that definite diagnosis of flutter is made possible only by resort to graphic methods. The most valuable graphic records are those obtained by the use of the Mackenzie polygraph and the electrocardiograph. A diagnosis is also made possible by the use of the fluoroscope.³⁰ However, fluoroscopy is of less value than the use of polygram or electrocardiogram, the electrocardiographic study being always the method of choice. A routine electrocardiogram should be taken on every patient entering the hospital, as otherwise many cases of flutter will be missed. The importance of this routine is emphasized by the fact that a flutter patient may present a normal pulse rate of regular rhythm, while, on the other hand, varying degrees of block may result in an irregularity of rhythm which may closely simulate auricular fibrillation.

30. Holmes, G. W., and White, P. D.: Auricular Flutter Detected by the Fluoroscope, *Jour. Am. Med. Assn.*, 1917, **68**, 844.

Electrocardiographic examination should not be limited to routine on admission, it should also be resorted to during course of treatment in order that one may note untoward effects of digitalis action, and the change of mechanism to fibrillation. That onset of fibrillation may not be recognized readily is shown by the fact that five members of the medical staff failed to note change in mechanism in this case at a time when onset of fibrillation had been shown by the electrocardiogram. It is worthy of note that during certain periods of fibrillation the pulse seemed to be less grossly irregular than during flutter with alteration in degree of block.

A combination of flutter and fibrillation, such as has been noted by Robinson,³¹ was not shown on any of our records.

THERAPY

The therapy indicated in auricular flutter is to endeavor to restore normal mechanism through the administration of digitalis. This change in mechanism is not direct; there usually occurs an interval period of auricular fibrillation.

If rate of ventricle is within normal limits and the circulation is well maintained, there is no indication for drug therapy. Thus in our patient the pulse rate fell to 60 shortly after admission, and remained between 60 and 80 as long as the patient remained in bed. During this period no digitalis was given. On slight increase of effort, however, it was found that there resulted an exact doubling of rate. After we had repeatedly observed this acceleration, we decided to begin digitalis, because the increased rate was higher than normal on the lowest plane of effort on which the patient could possibly live after leaving the hospital, and, consequently, continued proper maintenance of the circulation became doubtful. November 1, we began the administration of tincture of digitalis, 20 minims three times a day. After only 100 minims had been taken, the electrocardiogram showed periods of 3-1, 4-1 and 5-1 block, the latter being the highest degree of block noted up to that time, except under artificial vagus stimulation. November 4 (20 minims tincture of digitalis having been taken since November 1), the electrocardiogram showed distinct coupling with varying periods of block—2-1, 5-1. November 6 (320 minims taken), coupling was more pronounced and digitalis was omitted for two doses, then continued in the same dosage as before. On the 9th, there were long diastolic pauses, periods of 7-1 and 8-1 block, and coupling was so marked that we considered omitting the digitalis. Inasmuch as we had

31. Robinson, G. Canby: Relation of Auricular Activity Following Faradization of Dog's Atria to Abnormal Auricular Activity in Man, *Jour. Exper. Med.*, 1913, 28, 705.

not yet obtained the result for which we were striving, we decided to continue the drug under careful observation (Figs. 15 and 16). This course was followed until November 17, at which time the auricles began to fibrillate and the digitalis was discontinued (Fig. 17). A total of 940 minims (62.6 gm.) of the tincture had been taken over the period of seventeen days since treatment had been instituted. Except for the coupling and increased degree of block, there was at no time evidence of digitalis poisoning.

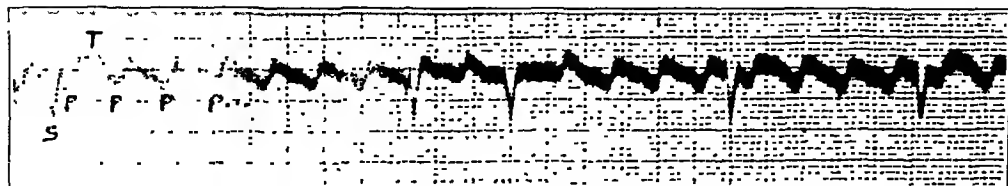


Fig. 15.—(No. 26, Lead II). Electrocardiogram showing increase in degree of block caused by digitalis. Taken after 460 minims tincture of digitalis had been given over a period of nine days. Note irregular ventricular response including 8-1 block.

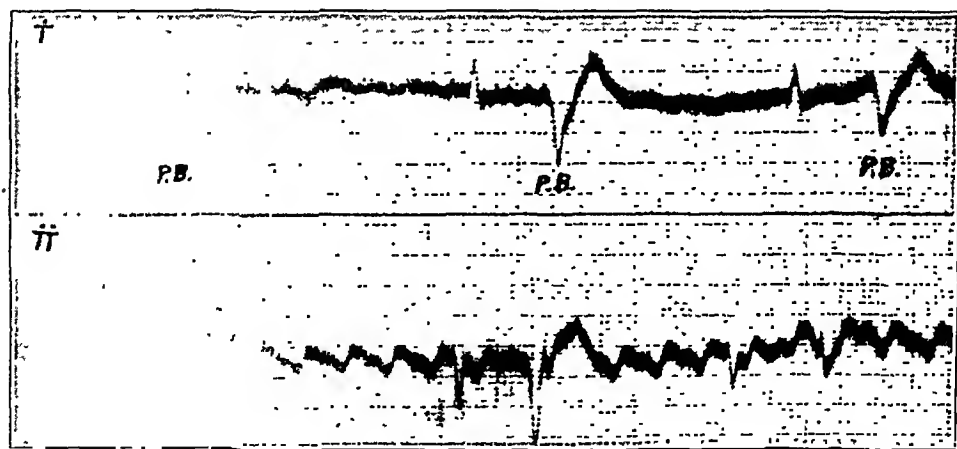


Fig. 16.—(No. 31, Leads I and II). Electrocardiogram taken after ingestion of 760 minims tincture of digitalis during a period of fourteen days. Marked digitalis coupling shown.

Of the fifty-three cases reported by Ritchie,⁵ only two had received larger doses than our patient, one receiving 1,455 minims in thirty-one days, the other 1,080 minims in eighteen days. Lewis¹⁰ reported two patients who received, respectively, 915 and 920 minims of tincture *strophanthus* (Cases 2 and 4). However, in each of these cases, the drug was discontinued because of diarrhea, and because, as Lewis says, there seemed no further prospect of producing auricular fibrillation. Each of these patients had been given, in a previous course, another member of the digitalis group, the drug having been stopped on account of nausea. Neuhof⁸ makes the statement, evidently without sufficient

proof, that the cases of flutter in which digitalis produces auricular fibrillation, later followed by normal rhythm, are those with marked decompensation. He says further, that since no decompensation was present in his case, he could scarcely have expected benefit from the digitalis. On this false premise he stopped the administration of digitalis when 10 drams had been given because "it was assumed that any further attempt to produce auricular fibrillation would be futile." Tallman³² emphasizes the importance of large doses and asserts that we must often give digitalis to the point of physiologic tolerance. He declares that the duration of flutter has apparently little effect on the amount of digitalis required.

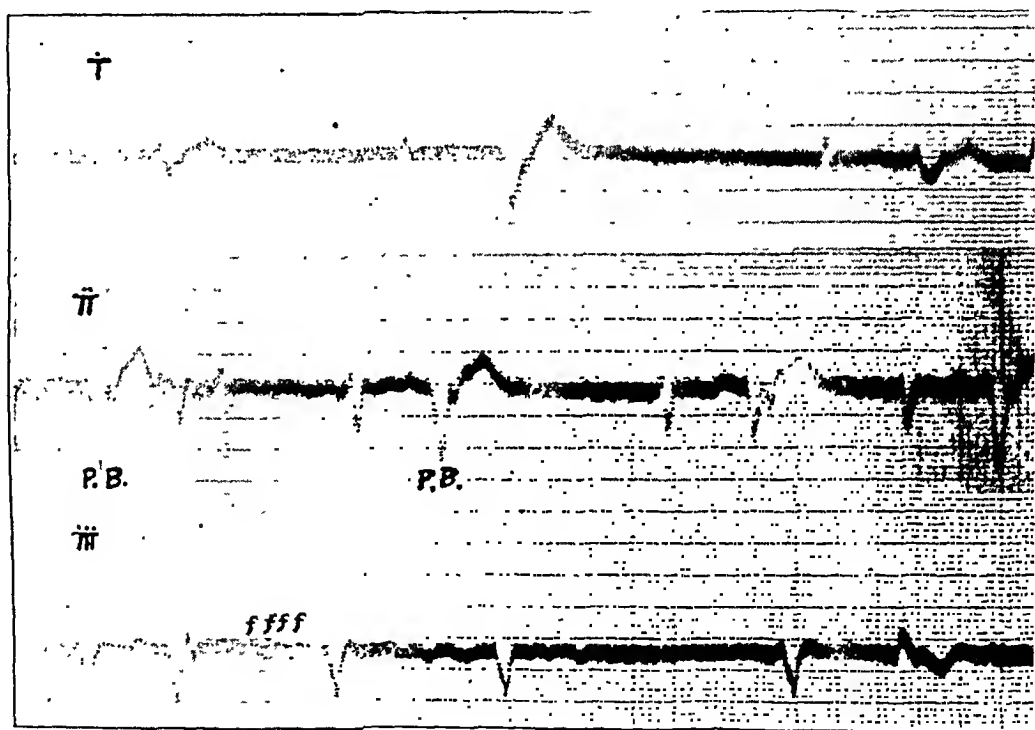


Fig. 17.—(No. 33, Leads I, II, III). Electrocardiogram taken after 940 minims tincture of digitalis had been administered over a period of seventeen days. The auricles are in fibrillation. Digitalis coupling is marked.

Cary Eggleston,³³ after careful tests, says that "the average therapeutic dose of digitalis given orally to man is 0.146 cat unit, or about 0.146 c.c. of an average high grade tincture per pound of body weight." In about half of his cases full therapeutic effects were secured with doses within 15 per cent. above or below this average. Furthermore, he says that "age, sex, and cardiac condition do not seem to influence the size of dose required." Taking this dosage as a standard, we gave

32. Tallman, M. H.: Auricular Flutter; Report of Cases, Northwest. Med., 1916, **15**, 145; abstr. in Jour. Am. Med. Assn., 1916, **66**, 1832.

33. Eggleston, Cary: Digitalis Dosage, THE ARCHIVES INT. MED., 1915, **16**, 1.

our patient, who weighed something under 180 pounds, about $2\frac{1}{2}$ times the average dose ($180 \times 0.146 \text{ c.c.} = 26.28 \text{ c.c.} = \text{"average dose"}$ our patient; actual amount given $= 62.6 \text{ c.c.}$). Eggleston says he obtained earliest therapeutic effects with large individual doses in thirteen hours, which is in conformity with the increase in block noted by us after 100 minims of the tincture had been taken in less than thirty hours.

The effect of digitalis on the T wave was interesting. During flutter, Lead I was the only lead in which the T wave was not obscured by the P waves, so we shall consider only the T of that lead. It is definitely upright and of an amplitude within normal limits on all plates taken up to the beginning of digitalis administration. After 200 minims of digitalis had been given, the T wave decreased in height. This effect, however, was not constant, since several plates taken during digitalis administration showed an amplitude equal to that noted before this drug was begun. After discontinuance of digitalis, the T wave was intermittently low during a period of eighteen days, after which period low waves did not reappear.

It is difficult to decide when the change in mechanism from flutter to fibrillation has been due to digitalis, since such change has occurred spontaneously. It is also difficult to know when the drug should be discontinued. Under ordinary circumstances, digitalis is stopped only with the onset of fibrillation. However, in our case marked toxic effect—coupling—was noted while the auricles still remained in flutter and after the administration of only 200 minims of the tincture. In view of the fact that our object—fibrillation—had not been attained, it was decided to disregard the warning, and our decision was subsequently justified by the fact that under continued use of the tincture no further toxic manifestations appeared, while the desired change in mechanism took place after the further administration of 740 minims of the drug. Digitalis was now discontinued, as observation has shown that a return to normal mechanism may be prevented by a further use of the drug after this stage in treatment. This return cannot be promised, for in but twenty-two of Ritchie's fifty-three cases was there a return to the normal mechanism. Such return has occurred as early as the third, and as late as the twenty-third day after digitalis has been stopped. It has now (at time of writing) been more than four months since we discontinued the first course of digitalis in our case, and four weeks since discontinuance of a second course. Fibrillation was still present when the patient was last observed, March 30. His apex rate was about 75, without pulse deficit. He returned to his work, using some caution in the amount of daily effort, and was without symptoms or physical signs of decompensation. If we can keep him in this state, with the possibility of return to normal, improbable though it be, we believe his condition to be better than when in flutter with the increased

rate on slightest exertion. In the chapter on treatment, Ritchie⁵ says: "We know that once auricular fibrillation is induced, there is a distinct tendency for it to persist. This is a most undesirable event." That it may not be wholly undesirable is shown by the result in our case.

In urgent cases, strophanthin, injected intravenously, has given excellent results. The other elements of treatment—rest, sedatives, treatment of causal factors—are based on the same principles as in other disturbances of cardiac mechanism and need not be considered here.

SUMMARY

A case is presented which shows most of the well known characteristics of auricular flutter.

The contour of the P deflection is discussed. We believe that in our case the P wave is diphasic, primarily downward, but that this is not a constant form in flutter. The origin of auricular impulses is believed to be ectopic.

The usual difficulties were encountered in the measurement of the A_s - V_s interval in flutter. We believe that in our case there was a marked variation of this interval. No constant variation was observed in relation to the varying degrees of block, although there was a suggestion of some difference in conduction time as the result of right and left vagus stimulation. The A_s - V_s interval was prolonged by digitalis in flutter as in normal mechanism.

Emphasis is laid on the variation of auricular rate as found in the individual case of flutter, a fact which has been usually overlooked.

Blood pressure studies showed marked daily variation of the systolic pressure as observed during flutter and fibrillation. There was a marked constancy of the diastolic pressure. Rather definite points were noted during fibrillation, in our case, corresponding to the systolic and diastolic pressures as taken in the usual manner during normal mechanism, an observation which led one of us to question the value of "average systolic" blood pressure readings in fibrillation.

Vagus stimulation by pressure, either over carotid artery or eyeball, produced ventricular slowing or standstill, as has been noted by previous observers. Pressure over the carotids was found to be the more reliable method, while better effects were noted with stimulation of the right vagus than of the left. However, this result was inconstant. In one instance an artificial Stokes-Adams syndrome was produced by vagus pressure. Latent period and residual effect after vagus stimulation were confirmed, as was the absence of effect on the auricle. Except for action on ventricular rate, no difference was noted between effects of right and left vagus pressure. Vagus stimulation produced like results in fibrillation and in flutter.

The prolongation of the refractory stage of heart muscle under the influence of repeated stimuli is noted as a possible explanation of the auriculo-ventricular dissociation in flutter and fibrillation.

Our case again emphasizes the necessity for the use of graphic methods in the diagnosis of flutter and of the transition to fibrillation.

Finally, the effect of digitalis during treatment—its very early effect on conduction, its possible effect on auricular rate, the change in the T wave, and the large amount necessary to change the mechanism to fibrillation — is considered at some length.

St. Francis Hospital.

CLINICAL STUDIES ON THE RESPIRATION

III. A MECHANICAL FACTOR IN THE PRODUCTION OF DYSPNEA IN PATIENTS WITH CARDIAC DISEASE *

FRANCIS W. PEABODY, M.D.

BOSTON

In a former paper¹ observations were reported on the effect of increasing the carbon dioxid content of the inspired air in normal persons and in patients with cardiac disease. It was shown that in normal persons the minute-volume of air breathed doubled when the concentration of carbon dioxid was between 4.2 and 5.4 per cent., and that cardiac patients, excepting those with a demonstrable acidosis, behaved in an approximately similar manner. In order to obtain further information as to the mechanism of dyspnea in heart disease additional observations have been made in which the subjects have been allowed to continue breathing until the carbon dioxid in the inspired air produced a high degree of dyspnea. It was hoped that at the height of dyspnea more difference would be found between the mechanism of the respiration in the normals and in the cardiac patients than was obvious when lower concentrations of carbon dioxid were being breathed. Such, indeed, has proved to be the case, and the demonstration of one of the abnormalities of the respiration in dyspneic cardiac patients forms the basis of the present communication.

METHOD

The method used has been described in detail in the paper referred to. Briefly it consists in having the subject breathe through valves which separate the expired from the inspired air. The expired air passes through a closed circuit and is then rebreathed, so that the inspired air contains a progressively rising percentage of carbon dioxid and a falling percentage of oxygen. Samples of the inspired air are then taken every two minutes and analyzed for carbon dioxid. A calibrated volumetric recording spirometer is connected with the closed circuit and the volume of each respiration is registered on the drum of a kymograph. With the aid of an electric timer, the minute-volume

* Submitted for publication April 30, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Medical School of Harvard University.

1. Peabody: Clinical Studies on the Respiration. No. 1. The Effect of Carbon Dioxid in the Inspired Air on Patients with Cardiac Disease, *THE ARCHIVES INT. MED.*, 1915, **16**, 846.

of air breathed can be thus easily determined. It will be noticed that in all instances the minute-volume at the beginning is unusually high. This is due in part to the fact that only a short time was given for the subject to accustom himself to mouth breathing, and in part it depends on the fact that the figures given are the actual measurements uncorrected for either temperature or barometric pressure. The subjects were either comfortably seated in a chair, or they were in bed, propped up with cushions in an erect position. The experiment was continued until the subject was so intensely dyspneic that he was unable to continue any longer. On breathing atmospheric air again dyspnea disappeared almost immediately and respiration became normal. In a few instances a troublesome headache persisted. As was to be expected, it was possible to continue the experiment longer, and thus produce a relatively higher degree of dyspnea in normal persons than in cardiac patients, since several of the latter were seriously sick. Only those have been selected for the present discussion, however, who showed a willingness and an interest in cooperation, and who persisted in continuing until they became extremely breathless.

NORMAL SUBJECTS

The four normal subjects were young men between the ages of 25 and 33 years. Only one (F. G. B.) had done much athletic work and he had not been in strict training for several years. Their response to

TABLE 1.—DATA AT BEGINNING AND END OF OBSERVATION
OF FOUR NORMAL SUBJECTS

Subject	Rate of Respiration		Single Respiration, C.c.		Minute-Volume, Liters		Per Cent. of Increase in Minute-Volume at End	Per Cent. of CO ₂ in Inspired Air at End
	Initial	Final	Initial	Final	Initial	Final		
D. W. C.	18	32	542	2,328	9.8	74.5	761	7.35
F. G. B.	16	25	592	2,980	9.5	74.4	786	9.08
F. W. P.	12	29	734	2,814	8.6	81.6	947	7.11
J. C. W.	17	30	627	2,260	10.7	67.7	635	9.22

the stimulus of the carbon dioxid was within normal limits, the initial ventilation being doubled by a concentration of carbon dioxid agreeing closely with that found for normal subjects in the previous paper. In Table 1 are the essential data at the beginning and at the end of the observation.

Reference to Table 1 as well as to the graphic records of the respiration (Figs. 1 and 2) during the experiments show that under the

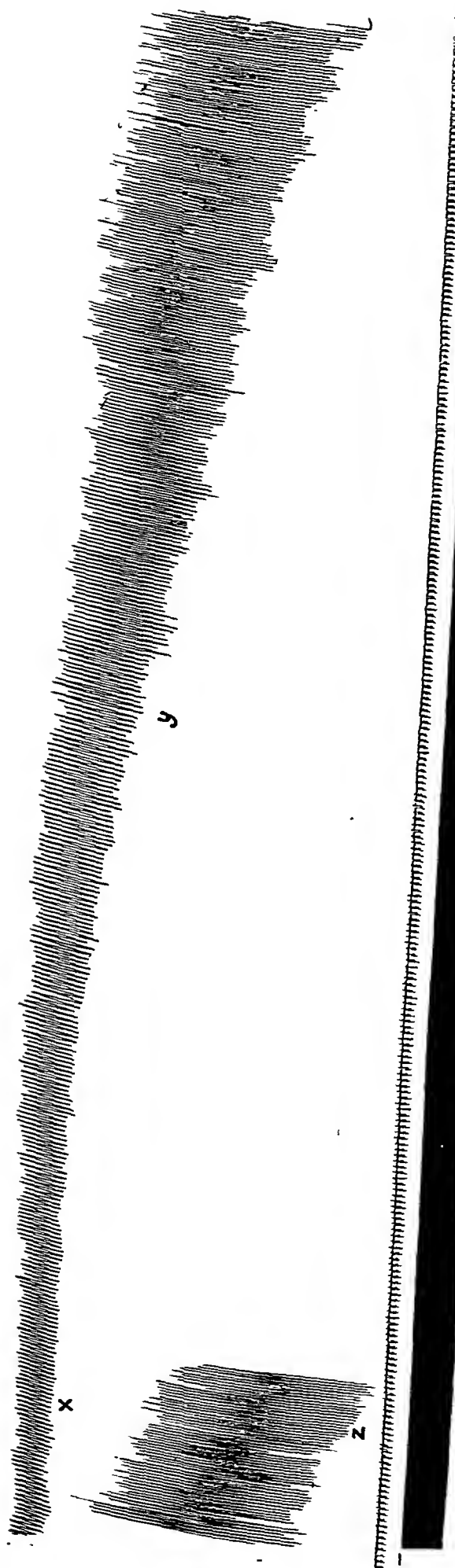


Fig. 1.—F. G. B.; normal. Sept. 30, 1915. At X (beginning) inspired air contained 0.45 per cent. carbon dioxide; minute-volume = 9.5 liters. At Y (after twelve minutes) inspired air contained 5.04 per cent. carbon dioxide; minute-volume = 18.4 liters. At Z (after twenty-four minutes) inspired air contained 9.08 per cent. carbon dioxide; minute-volume = 74.4 liters. Figures 1 to 6 are graphic records of the respiration of normal subjects and of patients with heart disease while breathing progressively increasing amounts of carbon dioxide. Inspiration is represented by a down stroke and expiration by an up stroke. The length of each stroke corresponds quantitatively to the volume of the respiration. The timer marks five-second intervals. All tracings are to be read from left to right.

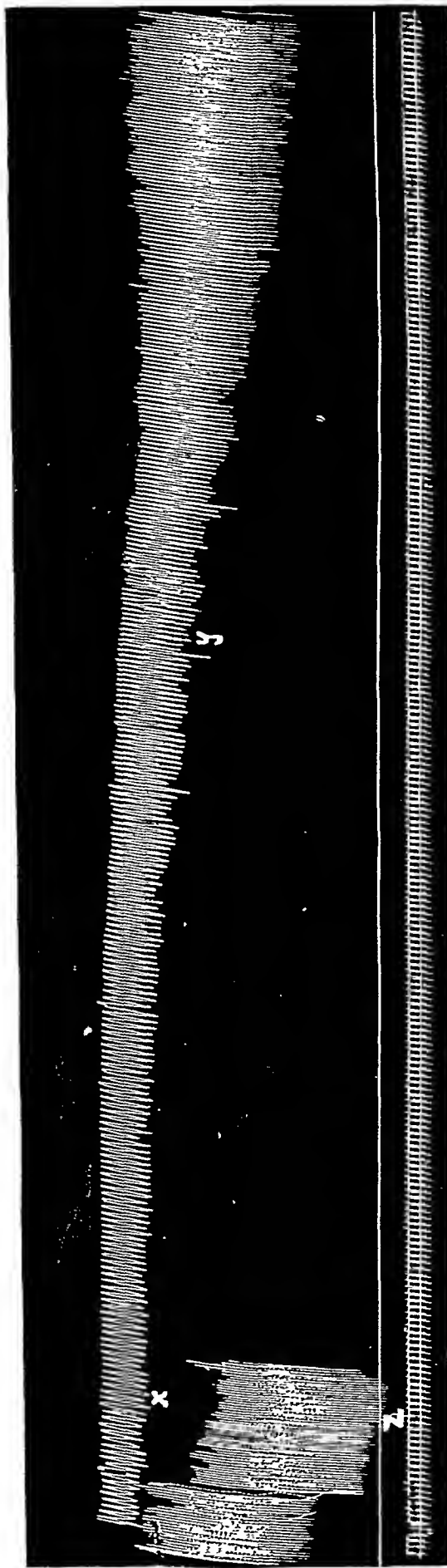


Fig. 2.—F. W. P.; normal. June 10, 1915. At X (beginning) inspired air contained 0.21 per cent. carbon dioxide; minute-volume = 8.6 liters. At Y (after twelve minutes) inspired air contained 4 per cent. carbon dioxide; minute-volume = 17.8 liters. At Z (after twenty-two minutes) inspired air contained 7.11 per cent. carbon dioxide; minute-volume = 81.6 liters.

influence of the rising percentage of carbon dioxid in the inspired air the minute-volume of air breathed increases, and that the increase in minute-volume is brought about by a rise in both the rate and depth of respiration. The average rate at the beginning was 16, and at the end it was 29 per minute. The average volume per single respiration was 624 c.c. at the beginning and 2,595 c.c. at the end. The average rate of respiration was thus nearly doubled, and the average depth was approximately quadrupled. The average increase in minute-volume, however, was nearly eight times that of the initial figure. The percentage of carbon dioxid in the inspired air at the time when the subjects were forced to stop on account of dyspnea varied from 7.11 to 9.22. The relation between the carbon dioxid in the inspired air and the percentage increase in minute-volume is not as definite with these high concentrations as it was found to be with the lower concentrations of carbon dioxid. J. C. W., who was breathing the highest percentage of carbon dioxid at the end of the observation, had the least increase

TABLE 2.—DATA AT BEGINNING AND END OF OBSERVATION OF FIVE PATIENTS WITH CARDIAC DISEASE

Subject	Rate of Respiration		Single Respiration, C.c.		Minute-Volume, Liters		Per Cent. of Increase in Minute-Volume at End	Per Cent. of CO ₂ in Inspired Air at End
	Initial	Final	Initial	Final	Initial	Final		
W. H. A.	15	20	589	1,164	8.8	23.3	264	4.27
W. E. M.	15	39	450	600	6.5	23.4	360	4.60
J. W. O'M.	15	36	10.2	25.9	254	4.97
J. S.	23	36	450	800	10.4	28.0	270	5.62
J. S.	25	26	475	900	11.7	23.4	201	4.97
W. E. W.	31	35	450	1,093	14.0	28.3	274	4.95

in minute-volume. This is especially noteworthy since much greater subjective symptoms were experienced by him than by the other subjects both during and after the observation. He was extremely dyspneic and was also troubled by dizziness, tingling of the hands and by a severe headache which began early in the course of the experiment and persisted for some hours after it was ended. Cyanosis was not marked. These symptoms were apparently due to carbon dioxid poisoning, and it seems probable that had he been able to keep his pulmonary ventilation higher he would have had less accumulation of carbon dioxid in the blood and tissues, and would have gone through the experiment with as little distress as did the other subjects who were able to regulate their respiration so that no excessive retention of carbon dioxid took place.

CARDIAC PATIENTS

There are six observations on five patients with cardiac disease which are suitable for the present study. All of them were severely afflicted subjects, in whom dyspnea was produced either by slight or by very moderate exertion.

Table 2 shows the data at the beginning and at the end of the various observations. J. W. O'M., J. S. and W. E. W. responded quite normally to the carbon dioxide, their minute-volumes being doubled by concentrations of carbon dioxide which would produce the same effect in normal persons. The other two subjects were more sensitive to the action of carbon dioxide. In the case of W. H. A., whose minute-volume became doubled while he was breathing air containing 3.64 per



Fig. 3.—W. H. A.; chronic myocarditis, auricular fibrillation. July 27, 1915. At X (beginning) inspired air contained 0.39 per cent. carbon dioxide; minute-volume = 8.8 liters. At Y (after ten minutes) inspired air contained 2.88 per cent. carbon dioxide; minute-volume = 14.7 liters. At Z (after fourteen minutes) inspired air contained 4.27 per cent. carbon dioxide; minute-volume = 23.3 liters.

cent. carbon dioxide, this is accounted for by the presence of a slight acidosis. The alveolar carbon dioxide was 36.3 mm. (Plesch method). W. E. M. doubled his ventilation when breathing between 2.3 and 3.0 per cent. carbon dioxide, but the cause of this increased sensitiveness is not apparent as there was no evidence of acidosis. He was, however, in poor condition and had been a long time decompensated.

A comparison of the respiration at the beginning of the experiment and at the height of the dyspnea shows several points of interest. The average rate of respiration was 21 per minute at the beginning (excluding W. E. W., in whose case it was 19) and 33 per minute at the end. The average volume per single respiration was 482 c.c. at the beginning and 911 c.c. at the end. Thus when the observation had

to be stopped on account of dyspnea the average rise of respiration rate was nearly as great as with the normal subjects, but the depth of respiration had only been doubled, while with the normal subjects it was fourfold the initial value at the end of the experiment. The result of not increasing the depth of respiration to a greater degree is still more strikingly shown when one considers the rise of the minute-

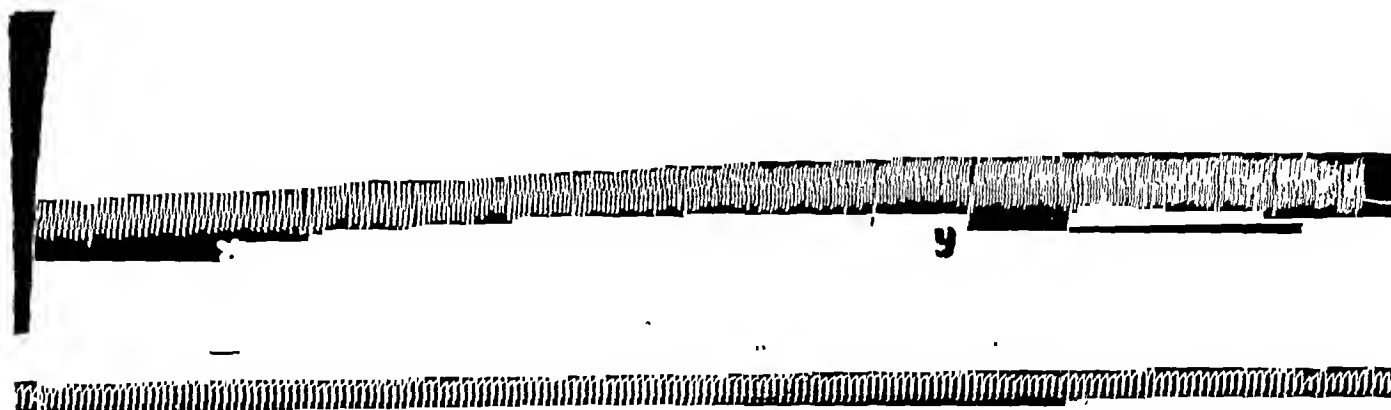


Fig. 4.—W. E. M.; mitral stenosis, auricular fibrillation. Dec. 26, 1914. At X (beginning) inspired air contained 0.18 per cent. carbon dioxide; minute-volume = 6.5 liters. At Y (after ten minutes) inspired air contained 3.07 per cent. carbon dioxide; minute-volume = 15.1 liters. At Z (after fourteen minutes) inspired air contained 4.60 per cent. carbon dioxide; minute-volume = 23.4 liters.

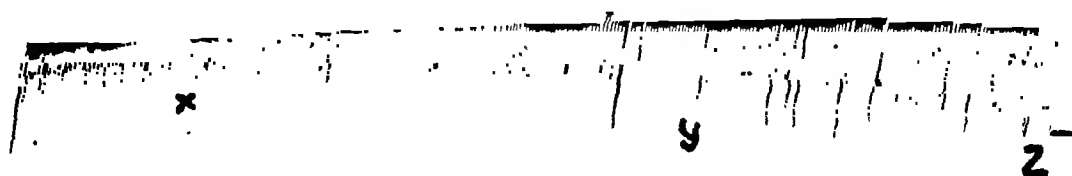


Fig. 5.—J. S.; mitral stenosis and insufficiency. Dec. 22, 1914. At X (beginning) inspired air contained 0.43 per cent. carbon dioxide; minute-volume = 11.7 liters. At Y (after eight minutes) inspired air contained 3.16 per cent. carbon dioxide; minute-volume = 18.1 liters. At Z (after twelve minutes) inspired air contained 4.97 per cent. carbon dioxide; minute-volume = 23.4 liters.

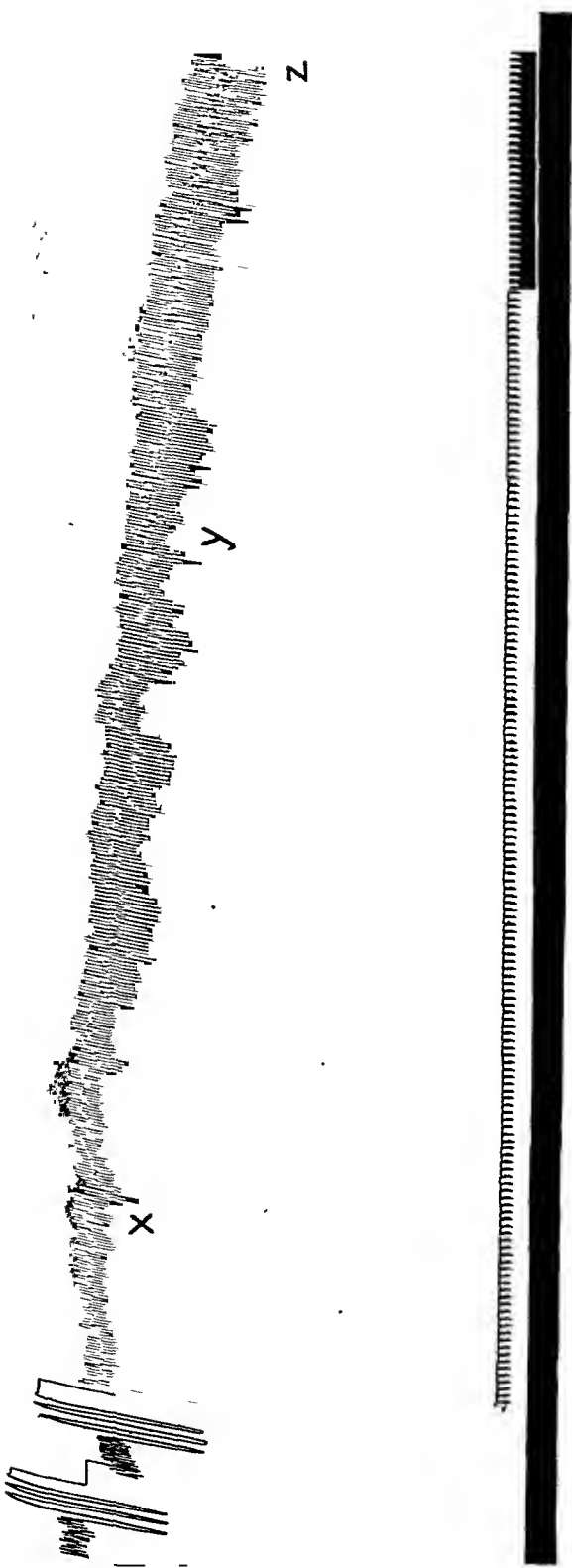


Fig. 6.—W. E. W.; mitral stenosis. Oct. 7, 1917. At X (beginning) inspired air contained 0.50 per cent. carbon dioxid; minute-volume = 14 liters. At Y (after ten minutes) inspired air contained 3.28 per cent. carbon dioxid; minute-volume = 20.2 liters. At Z (after fifteen minutes) inspired air contained 4.95 per cent. carbon dioxid; minute-volume = 38.3 liters.

volume. The average increase in minute-volume was approximately 800 per cent. with the normal subjects, but with the cardiac patients it was only 270 per cent. A comparison of the graphic records of the respiration (Figs. 3, 4, 5 and 6) made during the two sets of observations shows more clearly than do figures the differences in the respiration of the normal subjects and of the cardiac patients. From them it is quite evident that when the cardiac patients had to stop the experiment on account of dyspnea, they had increased the rate of respiration much as do the normal subjects, but the depth of respiration was increased to a much less degree. The percentage of carbon dioxid in the inspired air at the height of the dyspnea varied from 4.27 to 5.62. The cardiac patients thus became dyspneic when they were breathing a much lower percentage of carbon dioxid than was the case with the normal persons.

DISCUSSION

As the result of any stimulus to the respiratory center, whether, for instance, it is the carbon dioxid produced by the increased metabolism of exercise or whether it is a high percentage of carbon dioxid in the inspired air, the pulmonary ventilation becomes increased. There is, indeed, apparently a fairly close relation between the amount of the increase in ventilation as measured by the minute-volume of air breathed and the amount of the stimulus. As long as one can meet the demand for an increased ventilation easily and without undue exertion there is merely hyperpnea, but no dyspnea. The increased carbon dioxid is excreted normally and there is no accumulation in the blood and tissues. When, however, the stimulus to respiration is such as to require a greater ventilation of the lungs than the person can for any reason meet without undue exertion the subjective symptoms of dyspnea begin to develop. Thus anything that interferes with the normal ability to increase the minute-volume of air breathed tends to make the subject unduly sensitive to the development of dyspnea.

In the experiments just described, it was seen that under the influence of progressively rising amounts of carbon dioxid in the inspired air the rate and depth of the respiration of normal persons increased, until the minute-volume reached an average of approximately eight times its normal value. When the minute-volume had risen to this point the subjects were breathing as rapidly and as deeply as possible, and it was necessary to stop the experiment on account of extreme dyspnea. Patients with cardiac disease responded in nearly the same manner to the lower concentrations of carbon dioxid. A given amount of carbon dioxid produced about the same increase in pulmonary ventilation in the cardiac patients as it did in the normal subjects. They suffered from dyspnea, however, much more rapidly

than did the normal subjects and could not breathe such high concentrations of carbon dioxid, because they were unable to increase the minute-volume of air breathed to the same extent. In the cases studied dyspnea was experienced even when the minute-volume was only about two or three times its normal value. This inability to increase the pulmonary ventilation any higher is shown to depend on the fact that cardiac patients cannot increase the depth of their respiration as well as normal persons.

The essential difference between normal subjects and patients with heart disease with regard to the production of dyspnea is thus not that cardiac patients are necessarily more sensitive to any given stimulus to the respiratory center, but that they cannot stand as great a stimulus. Cardiac patients become dyspneic easier than normal subjects because they were unable to meet the rising stimulus to respiration with an adequate increase of pulmonary ventilation. The limitation of the depth of breathing is thus an important factor in the production of dyspnea in patients with heart disease. Rubow² has already made incidental references to this point in his article on "Die Kardiale Dyspnoe."

It has long been known³ that in many patients with heart disease the vital capacity of the lungs, that is, the volume of the greatest possible expiration after the deepest inspiration, is decreased below the normal. The demonstration in the observations reported here of the significance of the ability to breathe deeply in relation to the production of dyspnea has led to a detailed study on the subject of the vital capacity in patients with cardiac disease and its relation to dyspnea. The results of this investigation will be published separately.

2. Rubow: *Ergebn. d. inn. Med. u. Kinderh.*, 1909, **3**, 92.

3. Arnold: *Ueber die Athmungsgrösse des Menschen*, Heidelberg, 1855, p. 139.

CLINICAL STUDIES OF THE RESPIRATION

IV. THE VITAL CAPACITY OF THE LUNGS AND ITS RELATION TO DYSPNEA*

FRANCIS W. PEABODY, M.D., AND JOHN A. WENTWORTH, M.D.
BOSTON

INTRODUCTION

In an earlier paper¹ in this series, observations were described on the production of dyspnea in normal subjects and in patients with cardiac disease by means of increasing amounts of carbon dioxide in the inspired air. It was found that patients with heart disease became dyspneic more easily than did healthy subjects, and this tendency seemed to depend largely on their inability to increase the depth of respiration in a normal manner. A few preliminary determinations showed that this inability to breathe deeply corresponded to a diminished vital capacity of the lungs as measured by the volume of the greatest possible expiration after the deepest inspiration. Since any condition which limits the possibility of increasing the minute-volume of air breathed must be an important factor in the production of dyspnea, it appeared worth while to undertake an extensive study of the vital capacity of the lungs in those diseases in which dyspnea is a frequent symptom. The present paper deals with observations on the vital capacity in a large series of normal persons, of patients with heart disease and of patients with various other clinical conditions. Particular attention has been paid to the findings in cardiac disease because they appear to be of some practical significance. The results reported indicate that there is a very close parallelism between a decrease in the vital capacity of the lungs and the tendency to dyspnea.

HISTORICAL

No attempt will be made to give here a complete review of the literature which relates to the vital capacity of the lungs, but attention may be called to a few important contributions on the subject. In 1846 Hutchinson² reported a study of the relation of the vital capacity to the height in a large series of normal persons. In 1855 Arnold³ published an extensive and carefully compiled monograph on the vital

* Submitted for publication April 30, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Medical School of Harvard University.

1. Peabody, F. W.: See page 433, this issue.

2. Hutchinson, Jonathan: *Med. Chir. Tr.*, London, 1846, 29.

3. Arnold: *Ueber die Athmungsgrösse des Menschen*, Heidelberg, 1855.

capacity in health and disease. He studied the influence of age, sex, height, size and expansion of chest, and habit of life on the vital capacity, and showed that all of these factors may have considerable effect on it. The changes in the vital capacity in a number of pathologic conditions including heart disease are also described by him. Bohr⁴ in 1907 published his important investigation on the "Mittellage" of the lungs, including determinations of the residual, reserve and complementary air, the total lung volume and the vital capacity. The effects produced on them by changes of position, by exercise, by the inspiration of gases, as well as the variations met with in different persons are discussed in detail. Rubow⁵ measured the vital capacity in a number of patients in connection with his studies on the respiration in heart disease, but his chief interest was the change in the "Mittellage" of the lungs. Bittorf and Forschbach⁶ studied the lung volumes in pathologic conditions such as emphysema, heart disease and pleural effusions, and report with other data, the change in the vital capacity. Siebeck⁷ has made similar determinations of the lung volumes, and finds in accord with other investigators a low vital capacity of the lungs in heart disease.

METHOD

The vital capacity of the lungs is the volume of air which can be expired after the deepest possible inspiration. It was determined in these observations by means of a calibrated recording spirometer designed by Krogh.⁸ The movements of the spirometer with inspiration and expiration are written on the smoked drum of a slowly moving kymograph, and permanent records are obtained from which the volume of the respiration can be measured by the use of a graduated scale, with an accuracy of approximately 10 c.c. (Fig. 1). The subjects sit upright in bed or on a chair, and breathe in and out as deeply as possible through a rubber mouthpiece, the nose being closed by a tight clip. The spirometer was placed on a movable carriage, so that it could be taken to the bedside of patients whom it was not desired to bring to the laboratory (Figs. 2 and 3). No corrections were made for temperature, pressure, or water vapor tension.

No particular difficulty was experienced in obtaining satisfactory determinations of the vital capacity. Care was always taken to explain to the patients the desired object, and it was necessary to urge them to breathe as deeply as possible. Strict attention must be paid to this point, for otherwise the volume of the respiration is too low, and does

4. Bohr: *Deutsch. Arch. f. klin. Med.*, 1907, **88**, 385.

5. Rubow: *Deutsch. Arch. f. klin. Med.*, 1908, **92**, 255.

6. Bittorf and Forschbach: *Ztschr. f. klin. Med.*, 1910, **70**, 474.

7. Siebeck: *Deutsch. Arch. f. klin. Med.*, 1910, **100**, 204.

8. Krogh: *Skandin. Arch. f. Physiol.*, 1912, **27**, 100.

not represent the true vital capacity. As would be expected, the first attempt was often unsatisfactory, but the second or third attempt, after the subject had become accustomed to the apparatus, and after he appreciated what was required of him, almost invariably gave reliable results. The observations were made rapidly, and usually consumed only from three to five minutes for each person. In a small number of patients satisfactory results could not be obtained. This was either because it was impossible to make them understand what they were

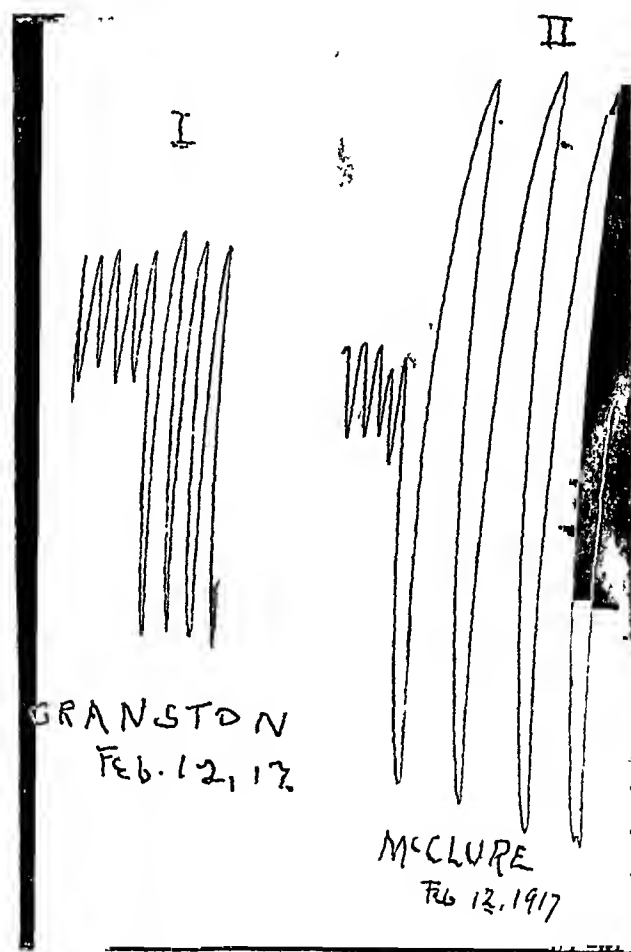


Fig. 1.—Records of vital capacity of the lungs: I, Patient with severe heart disease beginning to regain compensation; vital capacity was 2,500 c.c. or 52 per cent. of normal standard. II, Normal individual of about the same size; vital capacity was 4,620 c.c. or 96 per cent. of normal standard.

supposed to do, or because they were unwilling to cooperate. In such instances, it was, of course, necessary to discard the records. A little experience enables one to judge accurately as to whether or not the subject is actually breathing as deeply as possible.

Variations in the vital capacity as determined when sitting erect in bed or on a chair were small. Frequent observations have shown that the changes in vital capacity from day to day in normal persons, and



Fig. 2.—Recording spirometer, showing three-way valve and nose-clip.

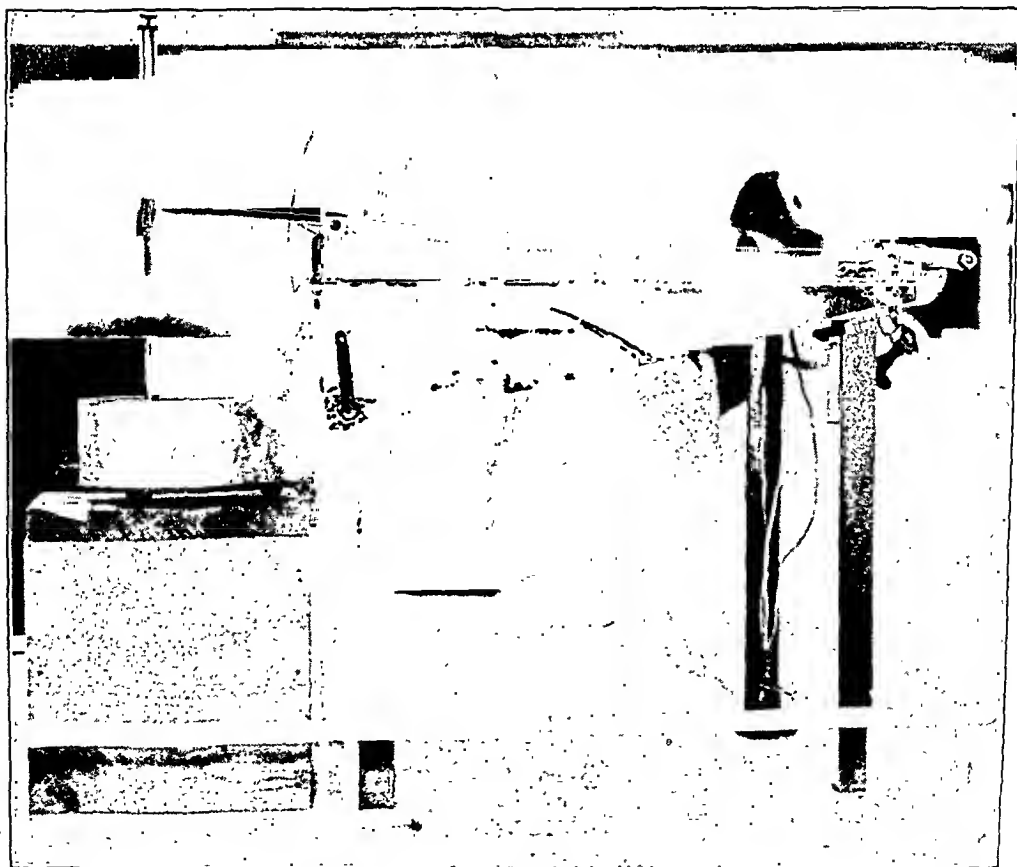


Fig. 3.—Recording spirometer, showing registering of respiration on drum of kymograph.

in patients whose clinical condition remains constant are practically negligible. The effect of posture was studied in two men. The vital capacity was first measured with the subject standing straight, and then again after he had assumed an exaggerated "slumping," round-shouldered posture in which the thorax acted at a great disadvantage. Such an extreme position is rarely met with, but the maximum difference in the vital capacity under the two conditions was only 590 c.c., or 12 per cent.

In order to simplify the technic of determining the vital capacity we have recently made use of a small portable spirometer of the ordi-



Fig. 4.—Portable spirometer, showing calibrated wheel at the top. This spirometer is made of copper and the bell is of aluminum.

nary type which holds 8 liters of air (Fig. 4). With this apparatus it is not possible to obtain graphic records, but the depth of respiration is measured directly on the calibrated wheel. The chief difference between this spirometer and the recording spirometer is that in the latter the subject breathes in and out several times, and since the lungs and spirometer form a closed system there is no chance for leakage, while with the former the subject takes a deep inspiration and blows it out into the spirometer. With an untrained person it would seem

possible that some air might be lost before the tube to the spirometer was inserted in the mouth. The two methods have been compared, however, by observations on a series of fifty normal persons and patients, and a strikingly good correspondence between them has been found. The greatest variation in the vital capacity by the two methods was 8 per cent., and in thirty-nine of the fifty persons studied the results agree within 5 per cent. The higher volumes were usually, but not always, obtained with the recording spirometer. It would thus seem that in the clinical study of the vital capacity of the lungs, where the highest degree of accuracy is not to be expected, a well balanced spirometer of the ordinary type may be used satisfactorily.

A. VITAL CAPACITY OF NORMAL ADULTS

In order to have normal standards of the vital capacity with which to compare the results obtained in disease, a study has been made of 140 healthy persons including physicians, nurses, medical students and a number of ward patients who would be classed as normal from the present point of view. The history of each person was investigated, especially with regard to any tendency to dyspnea, and in many instances a physical examination was made. The subjects ranged between 20 and 50 years of age, but the majority were between 20 and 30 years. They were on the whole a representative group of normal people in every day life. A limited number of observations was made on children, but not enough to give any reliable normal standards. It has, therefore, seemed best not to include any data on the vital capacity of children, either in health or in disease, in the present paper. Since it is generally known that the vital capacity decreases with advancing years, and since a number of the patients studied were over 50 years of age, it would have been better if it had been possible to study more elderly normal persons. Such subjects were, unfortunately, not easy to obtain; but in spite of this the normal standards established appear to be of practical value.

The vital capacity varies normally, as shown by Arnold, with many conditions. Age, sex, height, weight, the size and flexibility of the thorax and physical training may each and all influence it. It was felt to be important, however, in the present clinical study to have as simple a method of standardizing results as possible and, after attempting various ways, it was found that a classification based on sex and height was practical and sufficiently accurate.

In the determination of the normal standards of vital capacity, therefore, the observations on 140 normal persons have been grouped according to sex and for each sex three subgroups have been made on the basis of height. The average normal vital capacity has been determined for each subgroup. Having thus established the normal standards, it has been our custom to refer all subsequent determina-

tions to these and to express them in percentage of the appropriate normal.

Ninety-six normal males were studied and divided into three groups according to their height. Group I includes those who were 182.5 cm. (6 feet) tall or over, and the normal standard computed was 5,100 c.c. Group II consisted of men between 173.5 cm. (5 feet, 8½ inches) and 182.5 cm. (6 feet) tall, and the average vital capacity, which was 4,800 c.c., was taken as the normal. Group III was comprised of persons whose height was between 173.5 cm. (5 feet, 8½ inches) and 159.5 cm. (5 feet, 3 inches). The normal standard of this group was 4,000 c.c. With one exception the vital capacity in all the males examined varied between 86 and 121 per cent. of the normal figure, while 84 per cent. were within 10 per cent. of the normal. The largest vital capacity was 7,180 c.c., or 141 per cent. This was found in a powerful man (G. E. H.) who had recently been a member of the varsity crew, track and football teams in a large university. Four other members of this group had a vital capacity of 6,000 c.c. or over, and all had undergone severe athletic training. Table 1 gives the details of the determinations of vital capacity in the normal males and shows the actual and percentage variations from the standard adopted in each group. It will be noted that in Group I only 63 per cent. of the subjects had a vital capacity within 10 per cent. of the normal. This is explained in part by the small number of observations made in this group, but more particularly by the fact that many of these large men were highly trained athletes in whom one would expect to find the vital capacity unusually high. There was a difference of 2,150 c.c. between the highest and the lowest values obtained for the vital capacity in Group I, but if G. E. H., who is 190 cm. (6 feet, 3 inches) tall, be excluded, the difference is only 1,170 c.c. In Group II there was a difference of 1,500 c.c., and in Group III the difference between the highest and the lowest members is 1,630 c.c. There may thus be quite a variation in the actual vital capacity of normal persons of approximately the same height.

TABLE 1.—THE VITAL CAPACITY OF THE LUNGS OF NORMAL MALES

Group	Number Studied	Height in Feet and Inches	Normal Vital Capacity, C.c.	Number Within 10 per Cent. of Normal	Highest Vital Capacity	Lowest Vital Capacity	Highest per Cent.	Lowest per Cent.	Number Below 90 per Cent. of Normal
I	14	6' +	5,100	9	7,180	5,030	141	99	0
II	44	Over 5'8½" to 6'	4,800	41	5,800	4,300	121	90	0
III	38	5'3" to 5'8½"	4,000	31	5,080	3,450	127	86	1

Special attention is called to the last column in Table 1. It will be seen from this that only one of the ninety-six normal subjects had a vital capacity which was more than 10 per cent. below the appropriate normal standard. This is of particular importance from the standpoint of the present paper, since all of the pathologic conditions which affect the vital capacity produce a decrease of it. For practical purposes, then, the significant fact is the demonstration that healthy males almost invariably have a vital capacity of 90 per cent. or more of the normal standard. A decrease in the vital capacity below 90 per cent. will therefore suggest some pathologic condition.

The most important factor inducing extreme variation in the vital capacity of normal subjects of similar size appears to be athletic training. The average vital capacity of ten highly trained athletes was 120 per cent. of the normal standards. Table 2 shows the actual vital capacity, the percentage of the vital capacity in terms of the normal and a short note as to their athletic experience. The increase of vital capacity had persisted in some of them for several years after strenuous exercise had been last indulged in.

TABLE 2.—THE VITAL CAPACITY OF THE LUNGS OF TEN ATHLETES

Subject	Height in Feet and Inches	Vital Capacity, C.c.	Vital Capacity, per Cent of Normal	Training
G. E. H.	6' 3½"	7,180	141	Track team, football and crew, 4 years
P. W.	6' 2¼"	6,100	120	Cross country runner, 4 years
P. N. N.	6' 2"	6,100	120	Basket ball and track team, 4 years
H. M. R.	6' 1½"	6,000	118	Crew, much general athletics
A. M. G.	6' 1¼"	6,200	122	Hockey team, football team, crew
H. J.	5'11½"	5,800	121	Cross country runner
F. M. O.	5'11"	5,410	113	Football and track teams
N. R.	5'11½"	5,530	115	Football and track teams
F. C. H.	5'10½"	5,530	115	Cross country runner, 4 years
C. R. M.	5' 6"	4,690	118	Football team, 3 years; track team 4 years

The women were also subdivided into three groups according to their height. Group I was composed of those who measured over 167 cm. (5 feet, 6 inches) tall, and the average vital capacity was 3,275 c.c. Group II consisted of those who were from 162 cm. (5 feet, 4 inches) up to and including 167 cm. (5 feet, 6 inches). The normal standard for this group was found to be 3,050 c.c. Group III was made up of persons from 154.5 cm. (5 feet, 1 inch) up to and including those who were 162 cm. (5 feet, 4 inches) tall. The standard vital

capacity for this group was 2,825 c.c. Table 3 gives an analysis of variations from the normal standards in the different groups. Unfortunately, the number of female subjects studied is less than one half the number of males, and this may in part account for the greater percentage of variation from the normal. With a single exception the vital capacities were found to be between 86 and 124 per cent. of the normal. The highest vital capacity, which was 135 per cent., was found in a young woman who had been a student at a school for physical culture. Of the forty-four subjects, thirty had a vital capacity within 10 per cent. of the normal. As was seen to be the case with the normal males, however, only a very small number of females had a vital capacity below 90 per cent. of the normal standards. The lowest vital capacity was 86 per cent., and in but five instances did the vital capacity fall so low as to be between 86 and 90 per cent. of the normal.

TABLE 3.—THE VITAL CAPACITY OF THE LUNGS OF NORMAL FEMALES

Group	Number Studied	Height in Feet and Inches	Normal Vital Capacity, C.c.	Number Within 10 per Cent. of Normal	Highest Vital Capacity	Lowest Vital Capacity	Highest per Cent.	Lowest per Cent.	Number Below 90 per Cent. of Normal
I	10	Over 5'6"	3,275	5	4,075	2,800	124	86	2
II	13	Over 5'4" to 5'6"	3,050	9	3,425	2,600	112	88	2
III	21	5'4" or less	2,825	16	3,820	2,500	135	89	1

As far as our figures go, then, one may state fairly definitely that in normal persons the vital capacity is at least 85 per cent., and almost always 90 per cent. or more of the normal standards adopted for each group. In elderly persons a slight decrease from these standards may be expected.

Since it has been proved that the metabolism depends directly on the body surface area, it seemed to be of interest to discover whether some similar relation exists between the vital capacity and the body surface. In a series of nine cases the surface area has been calculated by the linear formula of Du Bois.⁹ From this limited number of observations it appears that there is a fairly constant relationship between the two, in persons of average build who have led approximately the same type of life as far as exercise goes. In highly trained subjects the ratio of the vital capacity to the surface area is higher than in less athletic persons. Table 4 shows the details of these observations.

9. Du Bois and Du Bois: THE ARCHIVES INT. MED., 1916, **17**, 863.

TABLE 4.—THE VITAL CAPACITY AND ITS RELATION TO BODY SURFACE AREA

Subject	Vital Capacity, C.c.	Vital Capacity, per Cent. of Normal	Surface Area, Square Meter	Vital Capacity per Square Meter Surface Area, Liters	Vital Capacity, Surface Area	Exercise
G. P. G.	4,000	100	1.57	2.55	26	Average
D. A. H.	4,410	110	1.65	2.67	27	Average
W. S. B.	4,710	98	1.73	2.72	27	Average
W. S. N.	4,770	99	1.77	2.70	27	Average
F. W. P.	4,800	100	1.83	2.62	26	Average
F. O. H.	5,360	112	1.87	2.87	29	Quarter mile runner
J. A. W.	5,080	106	1.87	2.72	27	Average
L. W. G.	4,500	94	1.88	2.39	24	Average
G. E. H.	7,180	141	2.12	3.39	34	Much athletics

If L. W. G. is excepted, the average vital capacity of the six men who were not athletes corresponded to 2.66 liters per square meter of body surface. Considerably higher values (2.87 and 3.39 liters) were found in the two athletes. Whether the relationship between the surface area and the vital capacity is actually more constant than is the relationship between height and vital capacity, will only be known after a much larger series of cases has been studied. For the determination of surface area the subject must be weighed stripped, so that unless a considerably higher degree of accuracy were to be obtained, it would be of advantage to maintain the simpler method. It is quite possible that the use of the linear formula for surface area would be valuable when dealing with persons who fall at the limits of two of the height groups. It is in these persons that the greatest deviations from the normal are usually found when height and sex alone are taken into consideration.

B. VITAL CAPACITY OF THE LUNGS IN HEART DISEASE

It has long been known that the vital capacity of the lungs is frequently decreased in heart disease. The present study, which is based on 224 observations on 124 patients confirms this fact, and shows in a striking manner that the clinical condition of the patient, and more especially the tendency to dyspnea varies very directly with the degree to which the vital capacity is diminished. Many types of heart disease are included, and for the present consideration no attempt has been made to differentiate them. The analysis of the results obtained from this considerable series of determinations is simplified if the patients are classified according to their vital capacity. In connection with

each group the various features of clinical importance will be discussed, and such deductions drawn as the observations appear to warrant.

Group I consists of cases with a vital capacity of 90 per cent. or more of the normal. There is thus no diminution below the accepted normal standard for the vital capacity. Twenty-five patients fall into this class. Very few of them complained of any symptoms referable to their hearts. Many of them entered the hospital for other diseases, and the cardiac condition was only found in the course of the routine examination. Dyspnea was no more prominent as a symptom in the histories of these patients than it would be found to be in a similar group of normal persons. Twenty-three of the cases in this group were able to work, and the majority without much restriction. Only two patients were prevented from working on account of heart disease. One of these (G. A.) had a low grade subacute endocarditis, but showed no dyspnea. The other (I. C.) was a neurotic person who complained constantly of precordial pain. It was impossible to tell whether or not the pain was actually due to cardiac weakness, but he was not encouraged to work. A third patient with mitral disease and evidences of hyperthyroidism (I. M.) gave a history of slight dyspnea on exertion, but she showed no breathlessness after climbing two flights of stairs rapidly with one of us. None of the patients in this group have died.

It is thus evident that cardiac patients with a vital capacity of 90 per cent. or more of the normal are almost invariably in a good state of compensation. They do not suffer from dyspnea after marked exertion, and if, as rarely happens, they are prevented from leading a normal life, this is usually on account of cardiac pain or some other disturbance.

Group II consists of cases in which the vital capacity falls between 70 and 90 per cent. of the normal. Forty-one patients, of whom twenty-four are males and seventeen are females, are included in this group. A history of dyspnea on moderate exertion was commonly given by these patients, but the majority could work, and the others with two possible exceptions, could lead a satisfactory, though somewhat restricted life. At the time when the observations on the vital capacity were made, twenty-two were working, four were ready to be discharged from the hospital, and eight were either at home or up and about the wards without symptoms of cardiac insufficiency. It will be well to make brief mention of the clinical condition of the seven remaining patients.

1. F. O., a blacksmith weighing 91 kg., had aortic insufficiency with a rapid heart and rapid respiration. He complained of dyspnea. His vital capacity, July 29, was 85 per cent. He was extremely nervous and his respiration became

much slower when he thought he was not observed. History states that he has had dyspnea for four years, but he admits that he has frequently been able to run up four flights of stairs without getting short of breath.

2. V. R. had cardiorenal disease. His vital capacity was 85 per cent. There was a history of dyspnea on exertion before he entered the hospital, but he has shown no tendency to dyspnea since his admission.

3. C. J. H. was an obese man with chronic myocarditis. His vital capacity was 76 per cent. There was history of dyspnea on exertion. There is no dyspnea at present.

4. A. O., a woman, had double mitral disease and auricular fibrillation. Her vital capacity was 74 per cent. There was slight dyspnea on walking about the ward, increased by going up stairs. She has been working as a clerk most of the time for a year since this observation. Her vital capacity is now 73 per cent.

5. I. C. had cardiorenal disease. There is history of dyspnea, but very little evidence of it in the hospital. Her vital capacity was 76 per cent. Six months later she reentered with uremia and marked acidosis and died. It is probable that some of the dyspnea on her first admission can be accounted for by an acidosis.

6 and 7. Two neurotic women, one of them obese, gave a history of dyspnea on exertion but showed little evidence of it when tested by exercising.

In general, then, it may be said that cardiac patients with a vital capacity of between 70 and 90 per cent. of the normal may have well marked heart lesions, but are usually able to lead a satisfactory although somewhat restricted life. About one half of the patients examined were actually at work, and many of the others were perfectly able to do a limited amount of work. One patient in this group showed signs of cardiac insufficiency even while leading a careful life. Only two patients have died, one of uremia and one suddenly, probably of acute cardiac failure or pulmonary embolism. On the other hand the members of this group differ from those with a higher vital capacity (Group I) in that almost all of them gave a history of dyspnea on moderate exertion, and have a distinctly limited cardiac reserve. A number of them have had periods of more or less severe cardiac decompensation in which there has been a further drop in the vital capacity. These cases are, therefore, to be regarded as border line cases in which the activities must be somewhat limited, but in which, under favorable circumstances, there is little evidence of cardiac insufficiency.

Group III consists of patients whose vital capacity is only from 40 to 70 per cent. of the normal. Sixty-seven patients, forty-one males and twenty-six females, fall into this class. The characteristic feature of this group is that all its members were in a much less favorable clinical condition than were those who had a higher vital capacity. Dyspnea on even moderate exertion was always noted in the history, and was, indeed, usually the most prominent symptom complained of. Even within the group there was a fairly definite relation between the vital capacity and the clinical condition. Thus all patients with a vital

capacity of from 40 to 45 per cent. of the normal were in bed. Some of them were slightly dyspneic even when completely at rest, while the others became dyspneic on the least exertion. With a vital capacity of from 45 to 60 per cent. of the normal, patients were rarely dyspneic while in bed, and most of them could walk slowly around the ward without becoming short of breath. A few were living at home and could come to the outdoor department, but they all had to walk slowly and avoided stairs or hills. When the vital capacity was between 60 and 70 per cent. the patients have usually been able to walk fairly comfortably, many could come to the hospital on foot, and could even go upstairs without any special distress. Only five (7 per cent.) of the persons in this group were at work when they were examined, and in all cases the work done was very light. Twenty-two (33 per cent.) were up and about the wards without symptoms, or were coming to the outdoor department, and twenty-four (34 per cent.) were still in bed at the time of examination. Eleven patients (17 per cent.) whose vital capacity has been found at some time to fall into this group have died. Only one patient, however, with a vital capacity of over 40 per cent., has died of uncomplicated heart disease in the hospital. E. M., who at one time had a vital capacity of 46 per cent., died four months later of uremia. A. C., with a vital capacity of 48 per cent. on April 7, 1916, died two months later of suffocation from a large aortic aneurysm. Five patients, all with a vital capacity which was so low that they only just fell into this group, died at home soon after leaving the hospital. Three others died in the hospital after showing a decrease in vital capacity below the limits of this group. Many of the patients who were discharged from the hospital in fairly satisfactory condition, but with a vital capacity of from 40 to 70 per cent., had entered the hospital on account of cardiac decompensation. At the time of admission they usually had a vital capacity which was below 40 per cent., or only slightly above this figure.

Thus cardiac patients with a vital capacity of from 40 to 70 per cent. of the normal are severely handicapped. They practically always suffer from dyspnea even on moderate exertion. Many of them can get about the house or can walk slowly on the street, but there are few whose activities are not very definitely limited, and only a small proportion are able to undertake any form of work. There is a fairly definite relation between the clinical condition of the patient and the vital capacity even within the group, and those with a vital capacity below 45 per cent. are usually forced to remain in bed. Attacks of severe cardiac decompensation occur with considerable frequency in this group of patients, and the mortality among those who have at some time been members of the group is rather high.

Group IV consists of patients with a vital capacity of 40 per cent. of the normal or less. Twenty-three cases, 11 males and 12 females, were studied in this group. They were all patients whose clinical condition was such that they had to remain in bed, and practically all showed evidences of cardiac insufficiency. Many were definitely dyspneic while absolutely quiet, and the others became short of breath on the slightest exertion. Eight patients whose vital capacity was below 30 per cent., had extreme dyspnea and orthopnea. The lowest vital capacity found was 17 per cent. There was a close relation between the clinical condition and the vital capacity, and as these decompensated patients improved there was a corresponding rise in the vital capacity. Thus G. G., a cardiorenal patient, entered the hospital with a marked orthopnea and a vital capacity of 30 per cent. He improved rapidly, and seven weeks later was at work. At this time his vital capacity had risen to 79 per cent. This is, however, an exceptional instance for only three patients who have at any time fallen into this group have subsequently recovered sufficiently to be able to work. It is of interest, too, that these were all patients undergoing their first break in compensation. The mortality in this group has been high, 61 per cent. of the cases having died. All of the other patients have remained chronic invalids, showing little clinical improvement after weeks of treatment.

Cardiac patients with a vital capacity which is 40 per cent. of the normal or less are usually bedridden and severely decompensated. Many of them have dyspnea even when completely at rest. Patients whose vital capacity falls as low as this during their first period of cardiac insufficiency may improve so much that they are able to return to a fairly normal life, but the occurrence of such a low vital capacity in later attacks of decompensation makes for a distinctly unfavorable prognosis. Few patients who have at any time fallen into this group have shown great clinical improvement, and more than one half have died.

Table 5 shows the mortality statistics, the number of patients showing evidence of marked decompensation and the number of patients working in each group.

It is evident then, in the light of the foregoing statements, that there is a remarkably close relationship between the clinical condition of cardiac patients, particularly as regards their tendency to dyspnea, and the vital capacity of the lungs. If the vital capacity be known, one can state with a considerable degree of accuracy what the functional condition of the patient probably is. It is, however, not at all surprising that certain exceptions to this rule are found, and that in occasional individual instances the determination of the vital capacity gives a misleading conception as to what may be expected of the sub-

TABLE 5.—THE RELATION OF THE VITAL CAPACITY OF THE LUNGS TO THE CLINICAL CONDITION IN PATIENTS WITH HEART DISEASE *

Group	Vital Capacity, per Cent.	Number of Cases	Mortality, per Cent.	Symptoms of Decom- pensation, per Cent.	Working, per Cent.
I	90+	25	0	0	92
II	70 to 90	41	5	2	54
III	40 to 70	67	17	89	7
IV	Under 40	23	61	100	0

* Certain cases were tested several times and, owing to changes in the vital capacity they appear in more than one group. In the "mortality" column they are included only in the lowest group into which they fell. "Symptoms of Decom-pensation" indicate dyspnea while at rest in bed or on very slight exertion. Under "Working" are included only those actually at work, and able to continue. Many other patients in Group II were able to work, but they are not included as they were still in the hospital.

ject. When one considers that age, body shape, habits of life, exercise and various other factors all tend to make the normal limits of the vital capacity very broad, it is only remarkable that these exceptions are not met with more frequently, and that such a constant correspondence may be found by what is a comparatively rough clinical test. The explanation of this seems to depend on the fact that the normal variations are usually in the direction of an increase above a certain average, while the pathologic variations are in the direction of a decrease. One type of case which may not conform to the general rule of the relation of clinical condition to average vital capacity is that in which the subject has formerly developed an unusually high normal vital capacity and has subsequently acquired heart disease. In such an instance the pathologic lesion in the heart may be associated with a considerable fall of the actual vital capacity, but the relative vital capacity, when compared to average normal standards, remains high. This brings us to a consideration of the changes in the actual vital capacity in the individual case. The various errors which result from the comparison of the individual to average normal standards are thus excluded, and, as might be expected, the variations found are of even more significance.

In many instances several determinations of the vital capacity of the same case have been made at intervals of days, weeks, or months, over long and short periods. The results of these observations may be rather briefly summarized. A very close relationship has been found to exist between the clinical condition and the vital capacity. Decom-pensated patients show a low vital capacity which rises as improvement begins, and the degree to which the vital capacity increases corresponds well to the degree of clinical improvement. When the vital capacity remains constant the clinical condition remains unchanged.

A rapidly rising vital capacity after a period of decompensation leads to a good prognosis, while failure to rise more than a small amount, and the maintenance of a continuously low vital capacity makes the outlook less favorable. Slight changes in the vital capacity of ambulatory cases may be of much significance. This is well illustrated by the case of J. S., a stained glass worker, who has double mitral disease and auricular fibrillation. When in his best physical condition his vital capacity is 2,600 c.c., or 65 per cent. of the normal. At such times he can walk slowly without discomfort, and can do a little light work. On May 1, 1916, he came to the outdoor department, stating that he felt poorly and found that he was getting out of breath more easily than usual. His vital capacity was found to have decreased to 2,000 c.c., or 50 per cent. He was given digitalis and told to go to bed for a week. On May 19, 1916, he reported again, to say that he was as well as before his upset, and his vital capacity had risen to 2,600 c.c.

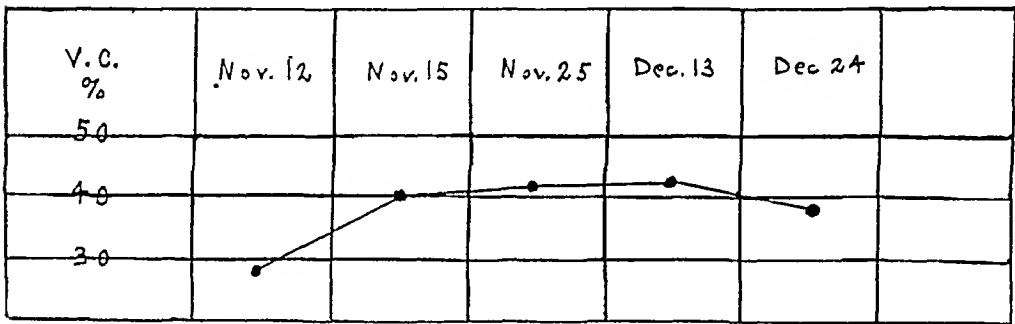


Fig. 5.—M. C. S., showing initial rise in vital capacity after acute cardiac decompensation. Subsequently, the vital capacity remained constantly low. General condition poor.

Figures 5 to 9 show graphically the variations in vital capacity associated with changes in clinical condition. On the basis of the observations as yet made, the impression is quite definite that such charts give a reliable index of the clinical course of the disease. In many ways they are more significant than records of the pulse rate or of the blood pressure, and it is our hope that an extensive routine application of the test of vital capacity may prove to be of distinct clinical value. Medical histories of patients with heart disease abound with vague statements about "dyspnea on exertion," and the increase or decrease of dyspnea, but these are usually only opinions based on the patient's story or on the gross observations of the physician. The importance of such statements would be considerably enhanced if they were confirmed by quantitative graphic methods. Whether, or in how far the determination of the vital capacity will actually fill this need, will only be known after a much larger series of observations than we have yet been able to accumulate has been made.

Two groups of cases, however, in which the determination of the vital capacity has been of service in correcting false impressions derived from the histories, deserve special mention. Several patients, especially women of rather neurotic temperament, have complained of shortness of breath which was apparently quite out of proportion to the physical findings in the examination of the heart, and the vital capacity has been so high as to afford no explanation for such a tendency to dyspnea. On the suspicion that the symptom was due to nervousness and was not true dyspnea, these subjects have been tested by walking rapidly and by climbing stairs. No abnormal dyspnea has resulted, so that the determination of the vital capacity served to con-

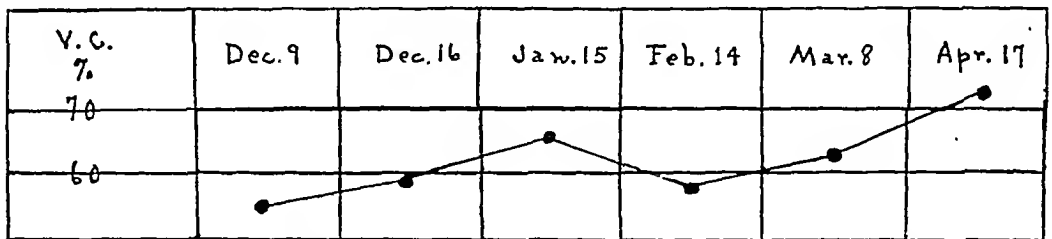


Fig. 6.—W. E. G. The fluctuations in the vital capacity correspond to changes in the clinical condition.

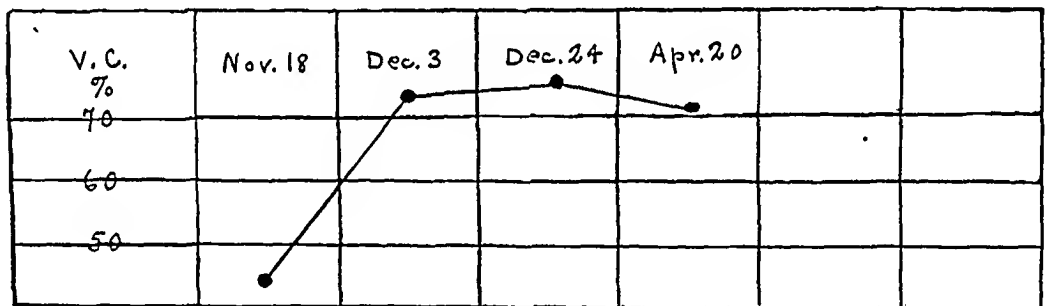


Fig. 7.—I. W. Marked rise in vital capacity, and continued good general condition after acute decompensation.

firm the physical examination, and the history, as given by the patient, could be fairly discounted. On the other hand, a few patients underestimate their respiratory discomfort on exertion. The vital capacity is lower than one would be led to expect from the history, and the lack of dyspnea is difficult to explain. Careful study of such a case, with exercise tests, may demonstrate that the patient's reserve is indeed much less than he has stated, and again the determination of the vital capacity has been a helpful check on the history. In other instances in which the history of dyspnea has seemed out of proportion to the results of physical examination the vital capacity has been low. In these patients the subsequent course has confirmed the value of the history and vital capacity, and has shown that physical examination gave an inadequate conception of the patient's reserve. Thus L. S.

had a vital capacity of 50 per cent. of the normal, but this was considered to be too low and as not representing her true condition. She never made much clinical improvement, however, and died of cardiac insufficiency some months later.

A careful analysis of the cases of heart disease with a view to finding whether there is any relation between the type of lesion and the decrease of vital capacity revealed little of importance. In general the vital capacity tends to be lower in cases with involvement of the mitral valves than in those in which the aortic valves are affected. This agrees with the common clinical observation that dyspnea is a

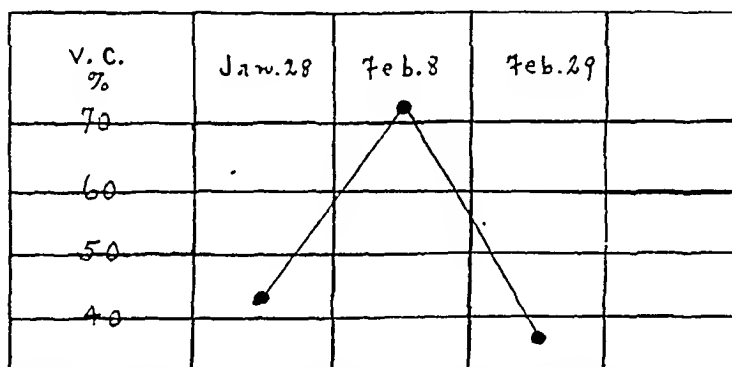


Fig. 8.—M. F. Rise of vital capacity after acute decompensation, and subsequent fall with another attack of cardiac failure.

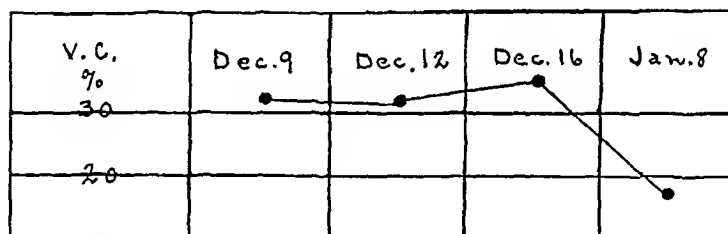


Fig. 9.—F. H. M. Low vital capacity in a patient with marked insufficiency, and further drop just before death.

more prominent symptom in mitral disease than in aortic disease. Beyond this the vital capacity of the lungs seems to depend on the degree of cardiac efficiency; on the severity of the lesion, rather than on the type of lesion.

Cause of the Decrease of Vital Capacity in Heart Disease.—Since the vital capacity of the lungs is the volume of air which can be expired after the deepest possible inspiration, it is evident that any condition which limits the movements of the lungs may be a factor in decreasing the vital capacity. In patients with heart disease a great variety of such conditions may be found. Some of these affect the movement of the chest wall and prevent a normal expansion of the thoracic cavity. Weakness of the intercostal muscles, rigidity of the

bony framework or ankylosis of the costal joints may act in this way. Alterations in the lung tissue itself may cause a diminution in its elasticity, as is seen in emphysema. Accumulations of fluid in the pleural cavities prevent the normal expansion of the lungs, and great cardiac hypertrophy, pericardial effusion or mediastinal tumors may produce a similar result. The normal inspiratory depression of the diaphragm is interfered with by intrathoracic conditions, which make it assume a flattened position even during quiet respiration, and by intra-abdominal conditions which push it upward. Hepatic enlargement, tympanites and ascites are examples of such conditions. Fluid within the bronchi and smaller air passages may prevent the entrance of air into considerable portions of the lung. This is, of course, frequently found in the dependent parts of the lungs in severely decompensated patients. The effect produced by a generalized bronchitis is not wholly clear from the results which we have as yet accumulated. The decrease in vital capacity associated with this condition is frequently much less than one would expect, and observations suggest that the intense dyspnea sometimes occurring in cardiac patients who acquire an acute bronchitis is largely dependent on some factor other than a change in the vital capacity.

In many cases, and particularly in acutely decompensated patients, conditions such as those just mentioned appear to account for the decrease in the vital capacity of the lungs in a wholly satisfactory manner. In other instances, especially where the examination of the heart gives little evidence of insufficiency, and where dyspnea is only experienced on moderate exertion, all of these factors may be absent, and yet the vital capacity may be low enough to fully explain the history of shortness of breath. The cause of the low vital capacity in such cases is not absolutely certain, but the work of Siebeck⁷ on the determination of the lung volumes in heart disease bears on the question and suggests that the decrease in vital capacity may be due to an overfilling or engorgement of the pulmonary vessels, and a consequent diminution of the elasticity of the lungs. If this is proved to be true it would signify that the determinations of vital capacity may give direct evidence as to the state of the pulmonary circulation. Such information would be of great value in the study of cardiac insufficiency. Other methods of examination bear chiefly on the greater circulation, and disturbances in the pulmonary circuit are only recognizable when of sufficient grade to cause the passage of fluid out of the vessels into the air spaces and the production of râles.

Experiments have been made to determine whether the decrease in the vital capacity in heart disease is apparent rather than real, and whether the inability to breathe deeply might depend on the rapid rate

of respiration. This would be the case, for instance, if an imperative stimulus to inspire should arise before the end of complete expiration. That this is, however, rarely, if ever, of importance is shown by the fact that patients with a low vital capacity may be able to hold their breath for several seconds at the end of either complete inspiration or of complete expiration.

DISCUSSION

The observations described above indicate that in patients with heart disease there is a close relationship between dyspnea and the vital capacity of the lungs. Thus, in general, patients with a vital capacity of 90 per cent. or more of the normal standard adopted for their sex and height have little or no abnormal tendency to dyspnea. Patients with a vital capacity of from 70 to 90 per cent. of the normal become short of breath on unusual exertion and must lead a restricted life, although many of them can do light work. Patients with a vital capacity of from 40 to 70 per cent. of the normal are much more limited in their activities. They become dyspneic on moderate or slight exertion, are rarely able to work and frequently suffer from cardiac decompensation. Those with a vital capacity of less than 40 per cent. of the normal are decompensated patients, usually confined to bed, and the mortality in this group is high. There is, moreover, a close correspondence in the individual case between changes in the vital capacity and variations in the tendency to dyspnea. In stages of decompensation the vital capacity falls, and with recovery the vital capacity rises. Indeed, comparatively slight changes in the patient's physical condition may manifest themselves in changes in the vital capacity. These facts confirm the evidence in a former paper regarding the importance of the decrease in vital capacity as a factor in the production of dyspnea in heart disease. Various obvious causes of decrease in the vital capacity, such as pleural effusion, emphysema and ascites, have been mentioned and the suggestion has been made that an important factor may be the distention of the pulmonary vessels owing to cardiac insufficiency. If this be true, then the determination of the vital capacity of the lungs may be of value as an early sign of cardiac weakness.

The importance of these observations depends on the relation between the vital capacity and the clinical condition of the patient. It is true that decrease in the vital capacity is only directly associated with a single symptom of heart disease. But this symptom, dyspnea, is a remarkably common one, and the intensity of dyspnea or of the tendency to dyspnea usually follows so closely the clinical course of the disease that it is not infrequently considered a guide to the con-

dition of the patient. It is, in a way, an index of the cardiac reserve, and thus, indirectly, a measurement of the efficiency of the heart. The degree of dyspnea and the tendency to dyspnea are, however, peculiarly difficult to describe accurately or to classify systematically, so that any objective method which will give even approximately exact evidence with regard to dyspnea merits serious consideration by clinicians. The determination of the vital capacity of the lungs, while lacking in absolute quantitative accuracy, is a simple proceeding which appears to do this. The changes in the vital capacity throw interesting light on the course, and often on the prognosis of the disease.

It is important, however, to appreciate that changes in the vital capacity of the lungs are an index of the clinical condition only in so far as the cardiac weakness manifests itself chiefly by causing dyspnea. This is very frequently, but not at all invariably the case. Certain patients with heart disease are restricted in their activities not by becoming dyspneic, but by the occurrence of palpitation or by pain. The vital capacity of the lungs has no direct connection with palpitation or pain, and therefore, in cases in which these are the presenting symptoms, it does not necessarily bear any relation to the clinical condition of the patient.

C. VITAL CAPACITY OF THE LUNGS IN VARIOUS OTHER DISEASES

Although the present study was directed chiefly to a consideration of the vital capacity of the lungs in heart disease, a comparatively large number of observations has been made in other clinical conditions. In some of these a tendency to dyspnea is a common symptom, and in others it is not. Such a series of observations is, of course, of great importance, for it shows in how far the various factors which decrease the vital capacity affect the production of dyspnea in conditions other than heart disease, and also in how far general muscular weakness is an element in causing a decrease of the vital capacity of the lungs. A brief summary of the results obtained in each disease is given below.

Bronchial Asthma.—Many patients with chronic asthma develop an emphysema, and associated with this they are subject to various degrees of dyspnea on exertion. It is thus not surprising to find that the vital capacity may be below normal even in the period between attacks. During the asthmatic attacks the vital capacity becomes much lower. Seven observations on six patients when they were in their best condition between attacks showed the vital capacity to range between 65 per cent. and 122 per cent. of the normal. In only one case was it below 85 per cent. This patient had suffered from asthma for twenty years, became dyspneic easily, and had never been able to do a full day's work. Four patients were tested soon after acute attacks

or at a time when many characteristic râles were present in the lungs. In three the vital capacity was 56, 60 and 85 per cent. The fourth, who stated that she had no dyspnea between attacks, had a vital capacity of 102 per cent. in spite of the presence of a few râles. For obvious reasons it was almost impossible to obtain records of the vital capacity during severe attacks of asthma.

Acute Bronchitis.—In three severe cases of acute bronchitis the vital capacity has not been diminished more than 10 per cent. In a fourth case of uncomplicated bronchitis in a young woman of 24 years, the vital capacity dropped to 76 per cent. of the normal. Objectively, she showed little evidence of dyspnea, but she complained of dyspnea. Several patients with cardiac disease have entered the hospital with extreme dyspnea and a well marked bronchitis. They have, however, not shown a decrease of vital capacity of more than 10 per cent. below the normal figure, and recovery has been rapid. It seems probable that the dyspnea in these cases was due to bronchitis and not to true cardiac decompensation.

Pleural Effusions.—This group includes cases with hydrothorax, pneumothorax, hemothorax, empyema and one instance of carcinoma of the pleura associated with a large pleural effusion. Nine patients have been studied. The vital capacity has been found to vary between 74 and 42 per cent. of the normal. In general the vital capacity seems to depend on the amount of fluid or air in the pleural cavity, and there is a close relationship between the decrease in the vital capacity and the tendency to dyspnea. Some of the patients were extremely sick, and their muscular weakness is probably a factor in lowering the vital capacity.

One patient (T. W.) with a pleural effusion that seemed to fill the left side of his chest, so that the lung was almost completely collapsed, had a vital capacity on two successive days of 48 and 49 per cent. Immediately after thoracentesis, with the removal of 2,200 c.c. of fluid, his vital capacity was still 46 per cent. On the two following days it had risen to 69 and 68 per cent., and three weeks later it was 74 per cent. At this time he could walk about the ward without any sensation of dyspnea, but there were still signs of fluid below the angle of the scapula on the left.

Pneumonia.—No records were obtained on patients during the course of the disease as the pain from the pleuritis makes it impossible for them to take a deep breath. In five convalescent cases, only one of which still showed evidence of pulmonary involvement, the vital capacity was between 71 and 114 per cent. The vital capacity was below normal in three cases, and in them general weakness, persisting after an acute infection, must be taken into consideration.

Cirrhosis of the Liver.—A patient with extensive edema and marked ascites had a vital capacity of 35 per cent. Another advanced case, with great ascites had a vital capacity of 35 per cent., rising to 61 per cent. after the removal of 10 liters of fluid. A man with early cirrhosis of the liver, without ascites, but giving a history of dyspnea on going upstairs (perhaps due to a weak heart) had a vital capacity of 85 per cent. Mechanical interference with the movements of the lungs is the essential factor causing dyspnea in these cases.

Nephritis.—In eight cases of acute nephritis without history of dyspnea, there was no decrease below the normal of the vital capacity. One other patient with acute nephritis, an Arab, had a vital capacity of 71 per cent., but it was impossible to get entirely satisfactory cooperation on the part of the patient, and it is doubtful whether he was breathing as deeply as he could.

In patients with chronic nephritis there is, of course, very frequently an associated involvement of the heart, but it is difficult to say in any individual case exactly how important this feature is. A considerable number of cases of chronic nephritis have been examined, some of them with and some of them without cardiac lesions. In those without evidence of heart disease, and without a history of dyspnea, the vital capacity was high and usually within the normal limits. In the cardiorenal cases, on the other hand, dyspnea was one of the prominent symptoms, and the vital capacity was usually decreased in proportion to the intensity of the dyspnea.

Certain patients with advanced renal disease have a much higher degree of dyspnea than can be explained on the basis of the decrease in the vital capacity alone. Not infrequently an examination of the blood or alveolar air will show a decreased carbon dioxid content. The dyspnea depends in part on an acidosis, and it may be relieved by alkali therapy.

Hyperthyroidism.—Dyspnea on exertion is one of the commonest symptoms complained of by patients with Graves' disease. This may sometimes be the result of nervousness, but it is usually an indication of cardiac weakness. Seven patients were tested, and the vital capacity was above 80 per cent. in five, while in two it was between 67 and 75 per cent. In all the decrease in vital capacity corresponded to the degree of the tendency to dyspnea.

Anemia.—Patients with anemia frequently suffer from dyspnea. Careful analysis of our series of cases, however, showed that weakness was a more common symptom, and in only five out of fourteen patients was a definite history of true dyspnea on exertion obtained. Eleven of these were typical cases of pernicious anemia, two probably due to carcinoma, and one was secondary to infect

Dibothriocephalus latus. In eleven cases the vital capacity was 80 per cent. or more, and in two others it was between 70 and 80 per cent. A very emaciated man of 66 years, who was considered to have advanced abdominal cancer, had a vital capacity of 65 per cent. The relation between the tendency to dyspnea and the decrease in vital capacity was not such as to make one consider that the latter was the chief factor in causing dyspnea. It seems more probable that dyspnea in anemia is due directly to the low hemoglobin content of the blood and is of a different mechanism from that in the other conditions which have been considered.

Diseases Unassociated with Dyspnea.—In contrast to the foregoing conditions, thirty patients have been tested who were in the hospital for conditions which are usually not associated with dyspnea. None of the mechanical factors which limit the movements of the lungs were present, and in them the effect of general debility and weakness could be studied. This group of cases includes acute and chronic arthritis, hemiplegia, diabetes, gastro-intestinal diseases, tabes, convalescents from acute infections such as typhoid fever and a number of persons in the surgical wards for slight operations. In twenty-four of the thirty cases the vital capacity was 85 per cent. or more, and in eighteen it was 90 per cent. or more of the normal. It will be well to make brief note of the six patients with vital capacity below 85 per cent. Three of them were diabetics. An emaciated decrepid old man of 69 years had a vital capacity of 63 per cent.; a second patient, so weak that he had to be helped up stairs, had a vital capacity of 76 per cent., and a third patient with diabetes for a year had a vital capacity of 68 per cent., but it was felt that his record was not satisfactory, and did not represent his true vital capacity. A woman, aged 66 years, who probably had peritoneal adhesions, complained of marked dyspnea on exertion and had a vital capacity of 78 per cent. A short man, aged 58, who had vertigo of an unknown cause, but who gave no history of dyspnea, had a vital capacity of 78 per cent. Finally, a young man of 23 years with a chronic synovitis of the knees was found to have a vital capacity of 84 per cent. of the normal. This subject was in bed for practically one year, and had then been on crutches for one year. He has used a cane up to within a week of the time he was tested, and stated that he still became short of breath on hurrying or on going up stairs.

As far as this comparatively small series of patients goes, then, it shows that in the ordinary cases in which dyspnea is not a prominent symptom, the vital capacity is usually within the normal limits. General weakness and debility may account for a slight decrease in the after-anacidity, but unless the weakness is extreme it usually does not

cause the vital capacity to drop more than 5 or 10 per cent. below the normal limits. Several patients in whom the vital capacity was below normal were over 50 years of age, and the decrease is in part explained by the normal fall in the vital capacity with advancing years.

SUMMARY

Determinations of the vital capacity of the lungs in a large number of healthy persons has made it possible to establish average normal standards for groups of individuals of different sex and height. When compared to the proper standard the vital capacity of healthy persons very rarely falls below 90 per cent. of the normal standard, although it may rise considerably above the normal.

Observations on patients with heart disease show that there is a close relation between decrease in vital capacity and the tendency to dyspnea. Compensated patients, who do not complain of dyspnea on exertion, have a normal vital capacity. Patients with more serious disease, in whom dyspnea is a prominent symptom, have a low vital capacity, and the decrease in vital capacity runs parallel to the clinical condition. Changes in the clinical condition are usually associated with changes in the vital capacity. As a patient improves, his vital capacity tends to rise, and as he becomes worse, it tends to fall. Determinations of the vital capacity in cases of cardiac disease are often of practical value as they give quantitative information as to the tendency to dyspnea, and thus, indirectly, as to the clinical condition and the reserve power of the patient.

In various other diseases in which mechanical conditions interfere with the movements of the lungs, the tendency to dyspnea corresponds closely to the decrease in the vital capacity. This is, however, apparently not true of the anemias. In diseases in which dyspnea is not a prominent symptom the vital capacity is usually within the normal limits, although general weakness and old age may cause a slight decrease.

CLINICAL STUDIES ON THE RESPIRATION

V. THE BASAL METABOLISM AND THE MINUTE-VOLUME OF THE RESPIRATION OF PATIENTS WITH CARDIAC DISEASE *

FRANCIS W. PEABODY, M.D., JOHN A. WENTWORTH, M.D.

AND

BERTHA I. BARKER

BOSTON

In a recent communication from the Russell Sage Institute of Pathology¹ the first satisfactory observations on the basal metabolism of patients with heart disease were reported. Sixteen patients with cardiac or cardiorenal disease were studied in the bed calorimeter at Bellevue Hospital, New York. An important result of the investigation was the close agreement found in the determination of the metabolism by the direct and indirect methods of calorimetry. Such an agreement, together with the finding of normal respiratory quotients, makes it probable that the metabolism in heart disease is not of an essentially abnormal type, and justifies the use of the indirect method in future work. It was furthermore shown that in patients with compensated cardiac lesions the metabolism was within normal limits, while in patients who had dyspnea while at rest in bed the metabolism was either normal or increased. "Of twelve patients with dyspnea, nine showed a distinct rise in metabolism, and in five of these the increase was from 25% to 50% above the average normal."

The work reported in the present paper is in part a continuation of that done at the Russell Sage Institute, as it seemed worth while to secure more data on so important a subject as the basal metabolism in heart disease. In part, however, it is an extension, for the method used allowed us to obtain information concerning the pulmonary ventilation, and the minute-volume of air breathed. This was of considerable significance to us, since one of the primary reasons which led to the study of heart disease was an interest in the mechanism of the production of dyspnea. It will be readily seen that the minute-volume of air breathed is an important factor in the investigation of patients from this point of view. The greater the amount of air which a patient breathes while at rest, the more limited he will be in his ability

* Submitted for publication April 30, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital, and the Medical School of Harvard University.

1. Peabody, Meyer and Du Bois: *THE ARCHIVES INT. MED.*, 1916, **17**, Part II, 980.

to increase his ventilation in response to the rising metabolism accompanying muscular exertion. Thus the greater will be his tendency to become dyspneic easily.

METHOD

The method used in the metabolism experiments was that of Tissot, the spirometer, valves and general technic being essentially as described by Carpenter.² Instead of the nose pieces, however, a rubber mask, recommended by Carpenter and made by the Siebe-Gorman Company for their mine rescue apparatus was used. This proved to be a distinct advantage, for the subjects could breathe either through the mouth, or nose according to their desire, and in getting reliable records of the minute-volume, it is, of course, essential that the respiration should be as natural as possible. In a few instances the mask could not be adjusted easily and a rubber mouth-piece was used, the nose being tightly clipped. The spirometer was of 100 liters capacity. The experimental periods were usually ten minutes long, but when the minute-volume was particularly high, they were necessarily of shorter duration. The inspired air was piped from outdoors to the inspiratory valves, so that there was no error, as might be the case if room air was used. The analyses of expired air were made with the Haldane portable gas analysis apparatus.³ The measured volume of expired air was reduced to standard conditions of temperature and barometric pressure, and the calculations were performed in the usual manner.

The metabolism as measured by the heat production in calories per hour was calculated from the oxygen consumption, use being made of the customary table which gives the calorific value of oxygen according to the respiratory quotient. The metabolism was then finally expressed in calories per square meter body surface per hour. The surface area was determined from the height and weight of the patient according to the chart of Du Bois and Du Bois.⁴ The average error of this simple method is ± 1.5 per cent., and the maximum error is only ± 5 per cent. Heat production varies of course normally, depending on the age and sex of the subject. The comparison of results in this series of observations has been somewhat simplified by the fact that all the subjects were males. For those between the ages of 20 and 50 years the normal standard of 39.7 calories per square meter of surface area, as given by Gephart and DuBois,⁵ has been assumed. For

2. Carpenter: A Comparison of Methods for Determining the Respiratory Exchange of Man, Pub. 216, Carnegie Institution of Washington, 1915.

3. Haldane: Methods of Air Analysis, Charles Griffin & Co., Limited, London, 1912.

4. Du Bois and Du Bois: *THE ARCHIVES INT. MED.*, 1916, **17**, 863.

5. Gephart and DuBois: *THE ARCHIVES INT. MED.*, 1916, **17**, 902.

older or younger subjects the average normals given by Du Bois⁶ for the various ages have been used. In the tables the metabolism is expressed in the percentage of the appropriate normal.

The general method of conducting the observations was as follows: The patient was brought to the laboratory on the afternoon before the day of the actual experiment. He was then shown the apparatus, the mask was put on his face, and the various experimental manipulations were run through with. This was found to be extremely important, as the subjects were naturally somewhat excited and anxious about what was going to take place. This preliminary trial, however, accustomed them to the method and reassured them completely. On the following morning they were brought to the laboratory in their beds, having fasted since the previous evening. After quieting down for about one-half hour, a record of the normal respiration was taken with a pneumograph. The mask was then adjusted and the metabolism experiment begun. When possible, three continuous ten-minute periods were run, but some of the more sick patients became fatigued after two periods, so that it was necessary to stop the observation. Pneumographic tracings were taken throughout each period, and the average rate of respiration counted. From the volume of expired air the average volume per single respiration was then calculated. The heart rate was counted, without the knowledge of the patient, by means of a stethoscope attached over the precordia.

The clinical condition of the patients on whom this report is based varied greatly. Some had slight valvular lesions, but were otherwise perfectly well, and had no evidence of cardiac decompensation. Others were seriously sick, and suffered from dyspnea and orthopnea. All were propped up in a semireclining position on bed-rests during the observation, but it has been shown that the metabolism is only about 3 per cent. lower in this posture than when lying flat on the back.⁷ It is obvious that it is extremely difficult to study the ventilation and the metabolism of patients who are dyspneic or who have a tendency to dyspnea. They are often easily worried by anything like a mask over the mouth or nose, and the psychic condition may alter the type of respiration profoundly. Many patients are wholly unsuitable to work with. The ones reported here are practically picked patients who were intelligent and anxious to cooperate with the work. We can feel reasonably certain that the results indicate the natural conditions.

In a former paper⁸ it has been shown that there is a close relation-ship between the tendency to dyspnea in cardiac patients and the vital

6. Du Bois: *THE ARCHIVES INT. MED.*, 1916, **17**, 887.

7. Soderstrom, Meyer and Du Bois: *THE ARCHIVES INT. MED.*, 1916, **17**, 872.

8. Peabody and Wentworth: See page 443, this issue.

capacity of the lungs. This is apparently so generally true that in those cases in which dyspnea is the predominating symptom — and this includes the majority of persons with heart disease — the vital capacity is a peculiarly accurate index of the clinical condition. Patients with a high vital capacity have little or no disturbance from dyspnea, while those in whom the vital capacity is below normal suffer from shortness of breath, and the degree to which they suffer depends largely on the decrease in vital capacity of the lungs. On this basis, then, it has seemed to be of interest in the present study to divide the patients into two groups according to the vital capacity. The first group consists of ten subjects with a vital capacity over 60 per cent. of the normal, according to the standards established by us. The members of this group were in comparatively good clinical condition, all of them being comfortable while at rest, and those whose vital capacity approached normal having little or no dyspnea even with moderate exercise. The second group consists of fourteen patients in whom the vital capacity was 60 per cent. of the normal or less. These were for the most part severely affected persons. Almost all of them became dyspneic on slight exertion, and those whose vital capacity was lowest tended to be dyspneic even while at complete rest in bed. It will be noted in the table that the average size of the patients in the two groups, as measured by their body surface area, is approximately the same.

RESULTS

The essential features of the various observations are shown in detail in the table. It is scarcely necessary to go into a discussion of the individual cases, as a consideration of the average findings in each group brings out clearly the more important results, and there are few significant deviations from the average.

Expired Air.—Analysis of the expired air shows that in Group I the percentage of carbon dioxide is higher and the percentage of oxygen is lower than in Group II. In Group I the carbon dioxide averaged 3.35 per cent. and the oxygen 17.04 per cent., while in Group II the carbon dioxide averaged 2.44 per cent. and the oxygen 18 per cent. Thus in the more severely affected patients the expired air approaches closer to the composition of atmospheric air, and one may say that the inspired air is less effectively used than normally. This is in harmony with the observations of Siebeck,⁹ who found that when cardiac patients were made to inspire pure hydrogen, the expired air in the dyspneic, decompensated cases contained a higher percentage of the inspired hydrogen than it did in normal persons or in compensated cardiac cases.

9. Siebeck: Deutsch. Arch. f. klin. Med., 1912, **17**, 252.

BASAL METABOLISM

Case No.	Hos- pital No.	Name	Date	Sur- face Area, Square Meters	Vital Capac- ity, C.c.	Vital Capac- ity, per Cent. of Normal	CO ₂ Tension, Mm.	Number of Periods	Analysis of Ex- pired Air		CO ₂ Pro- duc- tion per Minute, C.c.	CO ₂ Con- sump- tion per Minute, C.c.
									CO ₂	Oxygen		
1	4800	W. B.	7/11/16	1.73	4,710	98	3	3.17	17.52	189	209
2	4724	G. G. S.	6/29/16	1.55	2	3.24	17.09	183	229
3	4303	M. C.	3/21/16	1.98	3,750	94	3	4.15	15.69	227	304
4	4837	M. K.	7/ 7/16	1.94	3,700	93	2	2.72	17.77	184	225
5	4295	H. F. T.	3/23/16	1.59	3,770	79	2	4.01	16.58	198	221
6	4110	J. C.	2/18/16	1.65	3,170	79	2	3.98	16.22	202	252
7	4140	O. G.	2/21/16	1.70	3,700	77	2	3.38	17.36	203	221
8	5612	S. G. B.	11/17/16	1.64	2,750	69	3	2.70	17.50	149	202
9	5576	W. H. T.	11/11/16	1.69	2,600	65	3	2.80	17.66	190	234
10	4258	W. A.	3/ 7/16	1.71	3,050	64	2	3.36	17.04	230	280
Average.....				1.72	3,467	3.35	17.04	196	238
11	4373	J. J. McN.	3/28/16	1.96	2,410	60	3	2.77	17.51	207	271
12	4151	W. E. J.	2/14/16	1.57	2,280	57	3	2.17	18.50	194	227
13	4766	T. W. D	6/28/16	1.69	2,200	55	39.7* 40.7†‡	3	2.37	18.26	193	228
14	4262	G. A. L.	3/14/16	1.53	2,080	52	3	2.83	17.46	158	206
15	4963	F. W. B.	7/12/16	2.03	2,050	51	35.3†§	2	2.44	17.87	238	321
16	4414	S. B.	3/30/16	1.71	1,980	50	2	2.42	18.07	192	241
17	4264	C. G.	4/11/16	1.90	2,300	45	2	2.51	17.85	168	220
18	4275	G. G.	3/10/16	1.96	2,120	44	2	2.31	18.10	230	302
19	5795	M. F. M.	12/19/16	2.14	2,100	44	{30.6* 36.5†	3	2.99	17.16	239	323
20	4411	M. M.	4/ 4/16	1.75	1,990	42	2	2.75	17.52	210	277
21	4796	H. B.	7/ 3/16	1.71	1,950	41	3	2.59	18.02	198	232
22	5740	R. G.	12/ 9/16	1.56	1,640	41	30.4*	1	2.02	18.43	175	233
23	5704	C. N.	12/ 7/16	1.57	1,475	37	30.4*	1	1.91	18.80	221	259
24	4262	G. A. L.	3/ 2/16	1.70	1,200	30	30.4†‡	2	2.08	18.51	236	291
Average.....				1.77	1,984	2.44	18.00	206	259

* Carbon dioxid tension in alveolar air.
† Carbon dioxid tension in blood (Van Slyke method).
‡ These carbon dioxid determinations were made on June 4, 1916.
§ Blood carbon dioxid taken on July 4, 1916.
|| Blood carbon dioxid taken on March 4, 1916. Vital capacity had risen on this date to 1,470 c.c. (37.6 per cent.).

DETERMINATIONS

Respira- tory Quotient	Calories per Square Meter per Hour	Metabo- lism in per Cent. of Normal	Minute- Volume, Liters	Rate of Respira- tion per Minute	Aver- age Volume of Single Respira- tion	Diagnosis
0.904	35.7	10	6.03	12.7	475	Acute articular rheumatism; mitral insufficiency (?); no symptoms referable to heart
0.799	42.6	7+	5.71	13.4	426	Acute articular rheumatism; mitral insufficiency; heart completely compensated
0.747	43.7	10+	5.52	9.0	639	Chronic myocarditis; aortic insufficiency; mitral insufficiency and stenosis; recovering from decompensation; no dyspnea while in bed
0.818	33.6	5—	6.85	16.3	422	Chronic nephritis; chronic myocarditis and auricular fibrillation; about to be discharged after recovery from decompensation
0.895	44.1	7—	4.99	10.3	457	Acute articular rheumatism; acute serofibrinous pleurisy; chronic myocarditis; slight signs of cardiac insufficiency
0.802	44.0	11+	5.12	8.8	581	Mitral stenosis and insufficiency; auricular fibrillation; chronic arthritis; no evidence of cardiac insufficiency
0.919	38.6	3—	6.07	15.2	400	Mitral stenosis and insufficiency; auricular fibrillation; has recovered from an attack of decompensation and is about to be discharged from the hospital
0.738	35.0	0+	5.58	16.4	342	Chronic nephritis; chronic myocarditis and auricular fibrillation; moderately decompensated heart; walked to hospital on day before this observation
0.812	40.0	1+	6.87	17.6	392	Chronic nephritis with hypertension; chronic myocarditis with slight cardiac insufficiency; no dyspnea except on exertion
0.821	47.4	19+	6.91	12.0	574	Aortic insufficiency; mitral insufficiency; heart well compensated
0.826	2.5+	5.97	13.17	471	
0.764	39.4	12+	7.55	22.1	354	Chronic nephritis with hypertension; chronic myocarditis; recovering from acute attack of cardiac insufficiency; no dyspnea while in bed
0.855	42.3	4—	9.07	26.3	346	Mitral stenosis and insufficiency; three days after entering hospital with acute bronchitis; dyspnea on slight exertion; made a rapid recovery
0.847	39.4	1—	8.27	22.1	375	Mitral stenosis and insufficiency; auricular fibrillation; recovering from acute attack of cardiac insufficiency
0.767	38.5	9+	5.65	15.5	341	Chronic nephritis with hypertension; chronic myocarditis; recovering from acute decompensation; no dyspnea while in bed
0.741	44.9	27+	9.91	21.2	469	Chronic nephritis with hypertension; chronic myocarditis; acutely decompensated heart; much edema
0.797	40.6	2+	8.10	27.0	303	Chronic nephritis; syphilitic aortitis and aortic insufficiency; moderately severe decompensation
0.764	33.0	6—	6.78	19.0	355	Chronic nephritis and hypertension; syphilitic aortitis and aortic insufficiency; recovered from severe decompensation; no dyspnea on walking slowly
0.762	43.9	25+	10.10	22.0	479	Chronic nephritis and hypertension; chronic myocarditis; acutely decompensated with considerable dyspnea
0.744	42.8	22+	8.11	13.2	651	Chronic myocarditis and auricular fibrillation; acutely decompensated
0.758	45.1	14+	7.69	18.1	428	Chronic nephritis and hypertension; mitral stenosis and insufficiency; auricular fibrillation; acutely decompensated
0.854	39.4	3—	7.76	20.1	386	Aortic insufficiency; mitral insufficiency; recovering from severe attack of decompensation; no dyspnea while at rest
0.751	42.5	21+	8.81	25.5	346	Chronic myocarditis and auricular fibrillation; acutely decompensated
0.853	48.1	21+	11.80	25.4	465	Chronic nephritis and hypertension; chronic myocarditis; acutely decompensated
0.811	49.4	40+	11.60	27.9	413	Chronic nephritis and hypertension; chronic myocarditis; acutely decompensated
0.791	12.8+	8.59	21.8	408	

Carbon Dioxid Production and Oxygen Consumption.—In spite of the difference in the analyses of the expired air the actual production of carbon dioxid and consumption of oxygen per minute does not vary markedly in the two groups of patients. Both carbon dioxid production and oxygen consumption, however, and especially the latter, are somewhat higher in Group II, in which the expired air showed the lower carbon dioxid and the higher oxygen percentages.

Respiratory Quotient.—The respiratory quotients are normal in both groups of cases. The slightly lower quotient (0.79) in Group II corresponds to the higher consumption of oxygen in this group.

Basal Metabolism.—In Group I the metabolism averaged only 2.5 per cent. above the normal figure, and in only one instance (Case 10) was it essentially abnormal. The average metabolism in Group II was approximately 13 per cent. above normal, thus barely above the extreme limits usually set for the normal. Six patients in this group had metabolism of more than 20 per cent. above normal. These determinations of the basal metabolism agree satisfactorily with the results already referred to which were obtained with the large bed calorimeter at the Russell Sage Institute of Pathology. The patients who were in the best general condition (Group I) showed with one exception (Case 10) an essentially normal metabolism, while in the more severely decompensated patients the metabolism was sometimes normal, and sometimes considerably above the normal.

Minute-Volume of Air Breathed.—There is a rather striking difference in the minute-volume of air breathed by the two groups of patients. In Group I the minute-volume averaged about 6 liters, while in Group II it was slightly more than 8.5 liters. There is a general tendency for the minute-volume to be higher in the more severely decompensated members of Group II, in whom the vital capacity is lowest, but this relationship is somewhat obscured by the variation in size of the individual members of the group. G. A. L. was studied twice, first (Case 24) when he was severely decompensated, and later (Case 14) when he was in comparatively good condition and was quite comfortable while at rest. Between these two observations his vital capacity rose from 1,200 c.c. to 2,080 c.c., and his minute-volume fell from 11.6 liters to 5.65 liters, a drop of about 100 per cent. At the same time the basal metabolism showed a decrease of 31 per cent. It would, of course, be natural to associate the high minute-volume in the cases in Group II with an increase of metabolism, but scrutiny of the individual cases shows that such an association does not exist, and a comparison of the average results in the two groups of cases shows that the rise of the minute-volume in Group II is much more definite than is the rise of metabolism. In a few cases the low carbon dioxid

of the alveolar air or blood is evidence of an acidosis, but this is not of sufficiently high grade to account for the rise in minute-volume satisfactorily. This high minute-volume in severely affected cardiac patients has been observed by numerous other investigators among whom may be mentioned Beddard and Pembrey.¹⁰

Rate of Respiration.—As would be naturally expected, the rate of respiration is considerably higher in the patients whose clinical condition was worst. In Group II the average rate was 21.8, and in Group I it was only 13.2 per minute.

Volume per Respiration.—There is a definite difference between the two groups in the depth of respiration. In Group I the average volume per respiration was 471 c.c., while in Group II it was 408 c.c. Thus the respiration of the subjects of Group II was more rapid and more shallow than it was in the members of Group I.

SUMMARY AND DISCUSSION

Studies of the gaseous metabolism have been made in two groups of patients with heart disease. The subjects of Group I were in good or fairly good clinical condition, while those in Group II were for the most part more severely affected, being either decompensated and dyspneic while at rest in bed or becoming dyspneic on slight exertion. The basal metabolism was slightly higher in the patients of Group II. In some subjects of Group II the increase of metabolism was considerable, but this increase was not constant for all members of the group, and the average heat production per square meter of body surface was scarcely above the normal. On the other hand the minute-volume of air breathed averaged approximately 30 per cent. higher in Group II than it did in Group I, and individual instances were at least double the normal. Closely related to this are other observations which show that in the more seriously sick patients of Group II the rate of respiration is higher, the average volume of respiration is less, and the composition of the expired air approaches more closely to that of atmospheric air than was the case in Group I.

How are these abnormalities in the volume and composition of the expired air to be interpreted? Siebeck⁹ has made experiments which have a direct bearing on this subject, and which he explains on the basis that the inspired air is not thoroughly mixed with the alveolar air. Bronchitis, edema, areas of atelectasis, etc., prevent a complete diffusion of the inspired air throughout the lung, so that the efficiency of the respiration is decreased and the inspired air is less completely used than normally. This shows itself in the fact that the expired air

10. Beddard and Pembrey: Brit. Med. Jour., 1908, 2, 580.

has a high content of the inspired hydrogen in Siebeck's experiments and of oxygen in our own observations. In order, then, to obtain a sufficient amount of oxygen to supply the needs of the metabolism, a larger volume of air must be breathed. It is quite possible that an imperfect mixing or diffusion of the inspired air is a factor in the explanation of these observations, and it is easy to comprehend that such a condition may be present, but there is another feature that appears to be important. The two sets of patients whom we have studied were grouped according to the vital capacity of the lungs, those in Group I having a vital capacity of over 60 per cent., and those in Group II of 60 per cent. or less of our normal standards. Careful study of the minute-volume of the two groups of subjects shows a definite relation between this and the vital capacity of the lungs. In general, as the vital capacity falls, the minute-volume rises. There is, however, no distinct increase in the minute-volume until the vital capacity dropped to 60 per cent. or less of the standards which we have adopted as normal. If the vital capacity is below 60 per cent., the minute-volume is almost invariably increased. Case 14 is an apparent exception to this, but it is explained by the fact that G. A. L. is a small frail man, and the normal standard to which his vital capacity was referred is probably too high. His clinical condition was much better than has been the case with most patients having a vital capacity of only 52 per cent. of the normal, and he can fairly be considered an instance where the comparison of persons to general normal standards leads to an erroneous conception. Such exceptions are, of course, bound to occur.

In general, however, if the vital capacity is as low as 60 per cent. of the normal or less, the minute-volume of air breathed is above normal. Such a decrease in the vital capacity is considerable and is found usually only in rather severely affected patients. Many of the patients had obvious collections of fluid in the pleural cavities, or there was evidence of congestion and edema over the lower portions of the lungs behind, so that the available respiratory surface of the lungs was much diminished. For purposes of comparison with this group a patient may be mentioned with a pleural effusion which apparently filled one side of the chest so that one whole lung was practically completely thrown out. His vital capacity was 48 per cent. It does not seem illogical to assume that in these patients of Group II with much decreased vital capacity the respiratory surface is similarly diminished. The "dead space," however — nasopharynx, oropharynx, trachea, large bronchi, etc. — in which there is no respiratory exchange, probably remains essentially unchanged. The volume of each respiration is less than normal (408 c.c. in Group II as opposed to 471 c.c.

in Group I), but the dead space being unchanged, a much smaller proportion of each respiration reaches the alveoli. In order, however, that a normal or slightly higher than normal amount of oxygen shall be taken up by the blood in the alveolar walls, so as to keep pace with the metabolism of the body, the rate of respiration is increased. The expired air contains less carbon dioxide and more oxygen than normal, because it contains a larger proportion of air from the dead space.

The various abnormal findings in patients with severe heart disease can thus be explained on the basis of a decrease in the vital capacity of the lungs associated with a diminished respiratory surface. The volume per respiration is decreased, but the dead space is probably unchanged, so that the proportion of each inspiration remaining in the dead space is relatively increased. Oxygen supply is kept up by raising the rate of respiration, and in order that the alveolar ventilation may remain sufficient in spite of the relative increase of "dead space" the minute-volume of air breathed must be increased.

These observations on the increased minute-volume in patients with severe heart disease have a practical bearing on the production of dyspnea. If a normal person walks at a moderate pace the metabolism rises and the minute-volume is increased perhaps fourfold. With a patient in Group I it might thus rise from 6 to 24 liters. This is not a large amount, and a person with a normal vital capacity who can increase the depth of respiration easily would have no discomfort on breathing such a volume. If, however, one of the patients in Group II performed similar exercise, the minute-volume in his case, likewise rising fourfold, would amount to over 34 liters. This is much higher than it was with the more normal subject of Group I, and it thus is more difficult to maintain. It is, moreover, especially difficult for the subject in Group II, for his vital capacity is low and he cannot breathe deeply. It will thus be seen that the lower the minute-volume of air breathed at rest the less will be the tendency to dyspnea on exertion and the greater will be the patient's reserve. In like manner the slower the rate of respiration at rest, the greater will be the reserve. Thus an increase of the minute-volume of air breathed while at rest, and an increase in the rate of respiration while at rest, may both be factors in the production of dyspnea in heart disease.

CONCLUSIONS

Observations are reported on the gaseous metabolism and pulmonary ventilation of two groups of patients with heart disease. Group I consists of subjects in good or fairly good condition, in whom the vital capacity of the lungs was over 60 per cent. of the normal. Group

II consists of much more severely affected patients in whom the vital capacity was 60 per cent. of the normal or less.

The basal metabolism calculated from the oxygen consumption per square meter of body surface averaged 2.5 per cent. above normal in Group I, and 12.8 per cent. above normal in Group II.

The average volume per respiration was less in Group II than in Group I, and the average rate of respiration was higher in Group II than in Group I.

The minute-volume of air breathed averaged approximately 30 per cent. higher in the members of Group II than it did in those of Group I.

The relation is pointed out between the increase of the minute-volume of the more seriously affected patients and the decrease in the vital capacity of the lungs.

Finally it is shown that this high minute-volume is a factor in the production of dyspnea in persons with severe heart disease.

BOOK REVIEWS

A MONOGRAPH ON THE EPIDEMIC OF POLIOMYELITIS (INFANTILE PARALYSIS) IN NEW YORK CITY IN 1916. Based on the Official Reports of the Bureaus of the Department of Health. Published under the direction of the Department of Health of New York City. 1917.

To the many physicians throughout the country who followed with intense interest the poliomyelitis epidemic of 1916, this Monograph from the Department of Health of New York City cannot fail to be welcome. The size of the report—some 400 pages—would at first glance suggest redundancy, but one fails, in reading through it, to find anything which is not of interest and importance. Although compiled primarily from the standpoint of public health, all phases of the subject are well discussed from the purely scientific side as well, the attitude throughout being critical and conservative.

The first section, which is entitled "Historical," tells the story of the outbreak of the disease. The realization of the unusual severity of the epidemic, and the consequent emergency organization to study and control the disease, are related in detail. The arrangements for quarantine, publicity, and hospital care, the enrolment of special physicians and visiting nurses, the establishment of special poliomyelitis clinics, and the literature for lay distribution, may be mentioned among the many points to which attention was paid.

In the chapter on etiology are summarized both the pre-existing ideas as well as the points brought out by study of this epidemic. The finding of the virus in dust and sweepings, its resistant character, and the almost inescapable assumption of the intermediate human carrier, are discussed. A conservative statement of the status of the bacteriology of the disease is presented, and finally, the reemphasis by this epidemic of the paramount importance of the "abortive" or "nonparalytic" cases of the disease is dwelt on with due weight.

The chapter following, on epidemiology, considers in detail the various factors of possible importance in the spread of the disease. Season, sex, and age, sources of infection, food and milk supply, domestic animals as possible carriers, are discussed, and a separate section is devoted to a careful consideration of the possible association of insect carriers with the disease. The actual data of the epidemic are then presented, with charts, maps, and tables.

In the section on pathology one notes with special interest the frequent mention of nasopharyngeal lesions, which would harmonize well with the idea of transmission of the disease by the buccal secretions. In discussing the symptomatology, the importance is emphasized of the cases which run their course without paralysis.

The section on diagnosis presents an elaborate study of the spinal fluid findings. The increased cell count early in the disease, the late persistence of the globulin, and the colloidal gold curves are discussed. One is pleased to see that no rigid diagnostic claims are made, the interpretation of the findings in connection with the clinical picture being insisted on.

The chapter on treatment presents of course a disappointing record. The high mortality emphasizes the inability of the present therapeutic methods to cope with the disease even when recognized early. A thorough trial of all methods which seemed reasonable was, however, made, and one reads with particular interest of the studies on serumtherapy. As is, unfortunately, so often the case, a measure sound theoretically actually gives disappointing results, owing to such practical difficulties as that of getting the patients under treatment at the very onset.

The volume concludes with photographs and interesting charts illustrating the spread of the epidemic.

THE DIAGNOSIS AND TREATMENT OF ABNORMALITIES OF MYOCARDIAL FUNCTION; WITH SPECIAL REFERENCE TO THE USE OF GRAPHIC METHODS. By T. Stuart Hart, A.M., M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University. Price; \$4.50. Pp. 320. 248 illustrations. New York: Rebman Company, 1917.

Dr. Hart has made a definite contribution to electrocardiographic literature in this book. To the physician in hospital or general practice the variations in rate, rhythm and conduction are presented in an interesting and comprehensive manner. The preliminary discussion of cardiac physiology and pathology and their relation to graphic methods of registration furnishes the student with the information necessary for the proper interpretation of polygraphic and electrocardiographic records. A description of the instruments employed and of the details of their manipulation are available from other sources and have been wisely omitted by the author; so also have many theoretical considerations which still belong to the sphere of experimental cardiac pathology.

Bradycardia, tachycardia, heart block, extrasystoles, flutter and fibrillation are discussed with regard to their mechanism, experimental production, pathology, etiology, symptoms, identification and clinical significance. The presentation of the subject matter is clear and systematic. References are frequently made to the experimental data on which much of our knowledge is based. The clinical manifestations are constantly brought to the reader's attention and associated with the electrocardiographic picture.

The chapters on paroxysmal tachycardia, fibrillation and flutter are of particular interest. The close etiologic relationship between these three conditions is substantiated by electrocardiograms taken during the transition from one to another. The influence of right and left vagal stimulation on the cardiac rhythm is also well illustrated by graphic records. Bundle branch block, however, receives but passing mention and no electrocardiograms are included which show the atypical R waves associated with subendocardial lesions of the ventricular musculature.

In discussing sino-auricular block, phasic variation of rate and irregularities of the whole heart, the author does not agree with other investigators who believe that a partial or complete interruption of the excitation wave at the sino-auricular node may account for some of these phenomena. Since the publication of this book, Eyster and Meek have reported experiments in which partial sino-auricular block has been successfully produced in the dog's heart, confirming the view that in the human heart the sino-auricular node may be the seat of partial or complete obstruction. In view of these findings the interpretation of Figures 164 to 174 might bear revision.

The later chapters deal with the treatment of cardiac disease. Emphasis is placed on individualization in prognosis and treatment and on the conservation of myocardial reserve rather than on specific lines of therapy. The bibliography is carefully selected and classified. A conspicuous feature of the publication is the large number of excellent illustrations. The variety of conditions illustrated by polygrams and electrocardiograms is evidence of the wide experience of the author and demonstrates the importance of graphic studies in relation to the diagnosis and treatment of myocardial disorders.

The Archives of Internal Medicine

Vol. XX

OCTOBER, 1917

No. 4

A STUDY OF URIC ACID IN GOUT *

C. W. McCLURE, M.D., AND J. H. PRATT, M.D.

BOSTON

"Without uric acid, no gout," has been for many years a generally accepted dictum. And yet in spite of many investigations the relation of uric acid to gout has not been clearly established. In the diagnosis of gout by chemical means the same uncertainty exists. The uric acid may be increased in the blood and diminished in the urine, but the diagnostic value of these findings is doubtful. The development of new methods in biochemistry within the past few years permits a more thorough study of the factors governing the excretion of uric acid, and for this reason we have reinvestigated this subject.

Our studies on gout have been along the following four lines:

1. A comparison of the uric acid content of the blood in the gouty and in the nongouty.
2. The results obtained by the intravenous injections of uric acid in the gouty and in the nongouty.
3. A comparison of the exogenous output of uric acid by the gouty and the nongouty in feeding experiments.
4. The functional condition of the kidneys in gout. (This will be published as a separate study.)

I. THE URIC ACID CONTENT OF THE BLOOD

In 1913 Folin and Denis¹ introduced a colorimetric method for the determination of uric acid in small quantities of blood. Since our investigations were begun Folin has offered certain criticisms of his own method. Nevertheless, by its use data have been obtained which are of clinical interest in relation to gout. Different observers have

* Submitted for publication May 15, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Folin, O., and Denis, W.: A New Colorimetric Method for the Determination of Uric Acid in the Blood. *Jour. Biol. Chem.*, 1913, **13**, 469.

Pratt, J. H.: A Study of Uric Acid in the Blood in Gout by the Method of Folin and Denis. *Tr. Assn. Am. Phys.*, 1913, **28**, 387.

used modifications of the Folin and Denis method, but their reported figures in general seem too high to be comparable with those obtained by the use of the original method. For this reason we have not quoted the work of these authors, but only that of those using the method described by Folin and Denis.

The Uric Acid Content of the Blood in Nongouty Persons.—Figures for the quantities of uric acid estimated by the Folin and Denis method in the bloods of 381 nongouty persons have been collected from the literature.² In 314, or 82 per cent., the amounts of uric acid per 100 c.c. of blood ranged from 0.5 to 3.0 mg. Twenty of the latter number were normal persons, while the remainder represented cases of various organic disease, exclusive of gout, or cases with psychopathic conditions. Folin and Lyman³ found 4 mg. of uric acid in the blood of a healthy man who gave a family history of gout. Whether or not this patient should be grouped here as nongouty is a question of doubt. The amounts of urea and nonprotein nitrogen in the blood of this person were normal, so that there is no evidence for renal impermeability to other nitrogenous substances. Of the 156 psychopathic patients reported by Adler and Ragle⁴ the blood of thirty eight contained from 2.0 to 4.5 mg. of uric acid per 100 c.c. The number in which more than 3 mg. was present is not stated. Whether or not any of the cases were gouty or nephritic is not reported.

2. Folin, O., and Lyman, H.: On the Influence of Phenylquinolin Carbonic Acid (Atophan) on the Uric Acid Elimination. *Jour. Pharmacol. and Exper. Therap.*, 1913, **4**, 539.

McLester, J. S.: Studies on the Uric Acid of the Blood and Urine with Special Reference to the Influence of Atophan. *THE ARCHIVES INT. MED.*, 1913, **12**, 739.

Folin, O., and Denis, W.: On the Uric Acid, Urea, and total Nonprotein Nitrogen in Human Blood. *Jour. Biol. Chem.*, 1913, **14**, 29.

Folin, O., and Denis, W.: On the Creatinin and Creatin Content of Blood. *Jour. Biol. Chem.*, 1914, **17**, 487.

Kocher, A. R.: Ueber den Harnsäuregehalt des Blutes als Krankheits-symptom. *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 380.

Adler, H., and Ragle, B.: A Note on the Increase of Total Nitrogen and Urea Nitrogen in the Cerebrospinal Fluid in Certain Cases of Insanity, with Remarks on the Uric Acid Content of the Blood. *Boston Med. and Surg. Jour.*, 1914, **171**, 769.

Folin, O., and Denis, W.: The Diagnostic Value of Uric Acid Determinations in Blood. *THE ARCHIVES INT. MED.*, 1915, **16**, 33.

Pratt, J. H.: Studies on the Uric Acid in the Blood in Gout. *Am. Jour. Med. Sc.*, 1916, **151**, 92.

3. Folin, O., and Lyman, H.: See Footnote 2.

4. Adler, H., and Ragle: *Boston Med. and Surg. Jour.*, 1914, **171**, 769. See Footnote 2.

The bloods of the remaining sixty-seven, or 17.6 per cent., of the 381 nongouty persons contained from 3.0 to 10.0 mg. per 100 c.c. The diagnoses of these cases were:

- I. Chronic nephritis with and without uremia.⁵
- II. Arterial hypertension.⁶
- III. Acute and chronic types of nongouty and nontraumatic arthritis.⁷
- IV. Chronic lead poisoning.⁸
- V. Leukemia.⁹
- VI. Malignancy.¹⁰
- VII. Acute infections, especially lobar pneumonia.¹¹
- VIII. One case each of migraine,¹⁰ of renal calculus,¹² without nephritis, of mitral stenosis,¹³ and of puerperal toxemia¹⁴ in which the condition of the kidneys is not stated.

Obviously, the results obtained in the first three groups, which include nephritis and arthritis, are of most importance in determining the value of uric acid estimations in the blood as a means of differential diagnosis in gout. All cases of nephritis¹⁵ or of arthritis¹⁶ do not retain uric acid, in spite of the fact that in both conditions the blood may contain large amounts of nonprotein nitrogenous substances. Whether or not nephritis was present in the cases of arthritis in which retention of nonprotein nitrogen occurred in the blood, is not stated.

5. Folin, O., and Lyman, H.: *Jour. Pharmacol. and Exper. Therap.*, 1913, **4**, 539. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1913, **14**, 29. Kocher, A. R.: *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 380. Folin, O., and Denis, W.: *THE ARCHIVES INT. MED.*, 1915, **16**, 33. See Footnote 2.

6. McLester, J. S.: *THE ARCHIVES INT. MED.*, 1913, **12**, 739. See Footnote 2.

7. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1914, **17**, 487. Kocher, A. R.: *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 380. Folin, O., and Denis, W.: *THE ARCHIVES INT. MED.*, 1915, **16**, 33. Pratt, J. H.: *Am. Jour. Med. Sc.*, 1916, **151**, 92. See Footnote 2.

8. Folin, O., and Lyman, H.: *Jour. Pharmacol. and Exper. Therap.*, 1913, **4**, 539. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1913, **14**, 29. See Footnote 2.

9. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1913, **14**, 29. Kocher, A. R.: *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 380. See Footnote 2.

10. Kocher, A. R.: *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 380. See Footnote 2.

11. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1914, **17**, 487. Kocher, A. R.: *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 380. Folin, O., and Denis, W.: *THE ARCHIVES INT. MED.*, 1915, **16**, 33.

12. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1913, **14**, 29.

13. Folin, O., and Lyman, H.: *Jour. Pharmacol. and Exper. Therap.*, 1913, **4**, 539.

14. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1914, **17**, 487.

15. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1913, **14**, 29.

16. Folin, O., and Denis, W.: *THE ARCHIVES INT. MED.*, 1915, **16**, 33.

Of thirty-nine reported cases of nongouty, nontraumatic arthritis⁷ the blood uric acid varied between 1.2 and 2.7 mg. in thirty, or 77 per cent., and from 3.0 to 7.6 mg. in nine, or 13 per cent. In one of these cases¹⁷ the figures varied from 1.6 to 5.0 mg. and in another from 0.8 to 7.6 mg. Twenty, or 42 per cent., of fifty reported cases of nephritis¹⁸ showed from 1.0 to 2.9 mg. of uric acid per 100 c.c. of blood, and twenty-nine, or 58 per cent., from 3.3 to 10.0 mg. All of the above patients were receiving a purin-free diet at the time of the blood examinations.

Using the methods of Folin and Denis, we have determined the uric acid and the total nonprotein nitrogen in the blood of eight nongouty patients without clinical evidences of nephritis and in one case of advanced chronic nephritis. The findings are given in Table 1.

TABLE 1.—URIC ACID CONTENT OF BLOOD OF NONGOUTY PATIENTS

Case	Diagnosis	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein Nitrogen per 100 C.c. Blood	Diet of Patient
1	Dementia praecox.....	2.1	42	Purin-free
2	Dementia praecox.....	1.6-3.5	42	Purin-free
3	Senile dementia.....	0.8	39	Purin-free
4	Chronic nephritis, chronic ar- thritis.....	4.5	137	Purin-free
5	Chronic arthritis.....	2.2	...	Mixed
6	Chronic arthritis.....	2.4-3.3	32	Purin-free
7	Acute gonorrheal arthritis.....	2.0	40	Mixed
8	Chronic arthritis.....	1.8	28	Purin-free
9	Cirrhosis of the liver.....	1.7	40	Purin-free

The case of nephritis gave a high value for the blood uric acid. One of the cases of dementia praecox and one of chronic arthritis showed 3.5 and 3.3 mg. per 100 c.c. of blood, but on another examination less than 3 mg. were found. Our results agree with those collected from the literature and confirm the observation that the blood of the great majority of nongouty persons contains less than 3.0 mg. of uric acid per 100 c.c.

The Uric Acid Content of the Blood in Gouty Patients.—Of forty-nine reported cases of gout in which the uric acid in the blood was estimated by the method of Folin and Denis, thirty-eight, or 86.3 per

17. Pratt, J. H.: Am. Jour. Med. Sc., 1916, **151**, 92.

18. Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, **4**, 539. McLester, J. S.: THE ARCHIVES INT. MED., 1913, **12**, 739. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, **14**, 29. Folin, O., and Denis, W.: Jour. Biol. Chem., 1914, **17**, 487. Folin, O., and Denis, W.: THE ARCHIVES INT. MED., 1915, **16**, 33.

cent.,¹⁹ showed from 3.1 to 7.2 mg. per 100 c.c., and six²⁰ from 1.7 to 2.8 mg. All but six of the patients were on a purin-free diet prior to the uric acid determinations. In these six the blood contained from 3.1 to 5.2 mg. of uric acid per 100 c.c. of blood. Chronic nephritis was diagnosed in but two²¹ of the entire number of patients. In these the blood contained 3.1 to 5.7 mg. of uric acid. In seventeen of the cases²² the nonprotein nitrogen in the blood was determined. Less than 36 mg. were found in five, or 29.4 per cent., and 52 to 60 mg. in two, or 11.8 per cent.

Using the methods of Folin and Denis, we have determined the uric acid and nonprotein nitrogen content of the blood in the accompanying tabulated seven patients with gout (Table 2). All of these patients possessed tophi. Two were also suffering with chronic nephritis. The presence of nephritis was questionable in the other five patients, the only evidences being an occasional very slight trace of albumin or a scanty number of hyaline or finely granular casts. In one of the five patients cardiovascular disease was present.

TABLE 2.—URIC ACID CONTENT OF THE BLOOD IN GOUTY PATIENTS

Case	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein Nitrogen per 100 C.c. Blood	Diet of Patient
1*	5.1 4.8 57.0	Purin-free
2*	3.3	62.0	Purin-free
3	4.6 3.5 53.0	Purin-free
4	3.3	50.0	Purin-free
5	5.1 4.3 39.0	Purin-free
6	4.9	43.6	Purin-free
7	5.8	47.6	Mixed

* Patient had chronic nephritis.

More than 3 mg. of uric acid per 100 c.c. of blood were found in all cases. The nonprotein nitrogen of the blood was increased definitely above 50 mg. per 100 c.c. in the two patients with nephritis. No relation was found to exist between the amount of uric acid and the quantity of nonprotein nitrogenous substances in the blood. A

19. See Footnote 2.

20. Kocher, A. R.: *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 380. Pratt, J. H.: *Am. Jour. Med. Sc.*, 1916, **151**, 92.

21. Kocher, A. R.: *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 380. Folin, O., and Denis, W.: *THE ARCHIVES INT. MED.*, 1915, **16**, 33.

22. Folin, O., and Lyman, H.: *Jour. Pharmacol. and Exper. Therap.*, 1913, **4**, 539. Folin, O., and Denis, W.: *THE ARCHIVES INT. MED.*, 1915, **16**, 33.

review of the literature²² gives the same findings. The results obtained by our studies confirm the observations of previous writers¹⁶ and show that although in the majority of gout cases there are increased amounts of uric acid in the blood, a large percentage do not have markedly increased quantities of other nonprotein nitrogenous substances in their blood when on a purin-free diet.

We appreciate that the status of the method for estimating blood uric acid is unsettled. Nevertheless, on statistical evidence more than 3 mg. of uric acid per 100 c.c. of blood is a symptom of gout and is of especial importance when less than 50 mg. of nonprotein nitrogen is present.

II. EFFECTS OF INTRAVENOUS INJECTIONS OF URIC ACID

We have studied the effect of the intravenous injection of 0.5 gm. of uric acid on the quantities of that substance in the blood and in the urine. The method of procedure was to obtain the endogenous level of uric acid in the urine after the patients had been on a purin-free diet. Then the injection was made. Quantitations of uric acid in the blood were made on samples taken a few minutes prior to the injection, four hours afterwards, and then at twenty-four-hour periods. Estimations of the urinary uric acid were made in urine collected in several periods during the day of the injection and thereafter in urine collected for twenty-four-hour periods. The diet and analytical methods used are as follows:

Methods.—Patients were placed on a purin-free diet at least seven days before the injections of uric acid were made. The diet consisted of bread, cauliflower, potatoes, rice, cornflakes, the cereal preparations of wheat, lettuce, cabbage, tapioca, jelly, cream, butter, cheese, eggs, and sugar.

For purposes of injection 0.5 gm. of uric acid was dissolved in 30 c.c. of distilled water with the aid of 1 gm. of piperazine. The solution was sterilized in the autoclave at 10 pounds pressure for five minutes. It was found that autoclaving the solution for fifteen minutes under a pressure of 20 pounds of steam did not decompose the uric acid. Uric acid in the blood was determined by the original method of Folin and Denis¹ or by their modified procedure.²³ Nonprotein nitrogen was determined by either the original method of Folin and Denis²⁴ or by their later direct Nesslerization procedure.²⁵ Uric acid in the urine was quantitated by one of Folin's colorimetric methods:²⁶ In certain cases determinations were made with the uric acid phenol reagent by the method described in Folin's laboratory manual.²³ In other cases his uric acid reagent was substituted for the uric acid phenol reagent in this method. The latter reagent gives at times results which are slightly too high. Neverthe-

23. Folin, O.: Laboratory Manual of Biological Chemistry, New York, 1916.

24. Folin, O., and Denis, W.: New Methods for the Determination of Total Nonprotein, Urea and Ammonia in the Blood. Jour. Biol. Chem., 1912, **11**, 527.

25. Folin, O., and Denis, W.: Nitrogen Determinations by Direct Nesslerization. Nonprotein Nitrogen in Blood. Jour. Biol. Chem., 1916, **26**, 491.

26. Folin, O., and Denis, W.: On the Colorimetric Determination of Uric Acid in the Urine. Jour. Biol. Chem., 1913, **14**, 95.

less, we found that after feeding sweetbreads the results obtained in the same persons with the uric acid phenol reagent were fully comparable to those obtained with the uric acid reagent. In the descriptive tables, methods employed to quantitate uric acid will be designated in a footnote as the original method, the uric acid reagent method, and the uric acid phenol reagent method.

Intravenous Injections of Uric Acid Into Nongouty Persons.—Studies by previous observers on the excretion of uric acid in nongouty persons after its intravenous injection are given in Table 3. The experimental subjects were all on a purin-free diet.

TABLE 3.—PREVIOUS OBSERVATIONS ON THE EXCRETION OF INTRAVENOUSLY INJECTED URIC ACID BY NONGOUTY PERSONS

Observer	Diagnosis*	Exogenous Output of Uric Acid		Duration in Days of the Exogenous Output	Amount of Uric Acid Injected, Gm.
		Gm.	Per Cent.		
Bürger and Schwerfner ²⁸	1. Chronic arthritis	0.66	132	3	0.5
	2. Chronic arthritis	0.89	178	3	0.5
	3. Chronic arthritis	0.38	76	1	0.5
Umber and Retzlaff ²⁷ ...	3. Normal.....	0.40	80	4	0.5
	4. Normal.....	0.47	95	2	0.5

* The urine findings were normal in all instances.

Table 3 shows that after the intravenous injections into five nongouty persons the amounts of uric acid excreted varied. In two of the three cases of arthritis more uric acid was excreted than had been injected.

We have given five nongouty persons intravenous injections of 0.5 gm. of uric acid. Three of these were insane persons, and two had chronic arthritis. No evidence of kidney lesions was present in these patients, although complete renal function studies were made on but one. The findings of the uric acid injection experiments are given in the following protocols.

(PROTOCOLS FOLLOW)

PROTOCOLS

CASE 1.—J. M., Med. No. 5948, white, male, aged 32.

Diagnosis: Dementia praecox.

The patient did not use alcohol. The physical examination was negative. Blood pressure was 100 mm. systolic and 70 mm. diastolic. The urine examination was negative. Phthalein excretion was 60 per cent. in two hours. The patient was placed on a purin-free diet Oct. 29, 1915.

Date	Time of Collection	Urine			Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Nov. 1-2	9-9 a.m.	1,570	0.50	1.20			0.5 gm. uric acid intravenously
2-3	9-9 a.m.	1,820	0.50	0.97			
3-4	9-9 a.m.	2,810	0.61	1.26			
4-5	9-9 a.m.	3,995	0.54	1.21			
5	9 a.m. - 12 N.	370	0.08				
	12:15 p.m.	3.50	
	12 N. - 4 p.m.	250	0.09				
	4:15 p.m.	2.90	
5-6	4 p.m. - 12 N.	935	0.43				
	12 N. - 12 N.	1,215	0.54	0.98			
6	4:15 p.m.	42.00	2.10	
6-7	12 N. - 12 N.	2,420	0.71	1.25			
7	4:15 p.m.	1.70	
7-8	12 N. - 12 N.	2,550	0.66	1.37			
8	4:15 p.m.	2.50	
8-9	12 N. - 12 N.	2,250	0.66	1.06			
9	4:15 p.m.	1.6	

Endogenous output of uric acid, November 2 to 5=2.15 gm.

Endogenous output of uric acid per day=0.54 gm.

Per cent. of injected uric acid excreted=82 per cent.

Uric acid determinations made by the original method.

CASE 2.—E. S., Med. No. 5510. White, male, aged 41.

Diagnosis: Dementia praecox.

The patient was not an alcoholic. The physical examination was negative. Blood pressure was 140 mm. systolic and 95 mm. diastolic. The urine examination was negative. Phthalein excretion was 65 per cent. in two hours. The patient was placed on a purin-free diet on Oct. 29, 1915.

Date	Time of Collection	Urine			Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Nov. 1-2	9-9 a.m.	1,595	0.71	1.77			
2-3	9-9 a.m.	2,525	0.69	1.31			
3-4	9-9 a.m.	2,415	0.78	1.50			
4-5	9 a.m. - 7 a.m.	2,680	0.56	1.50			
5	7 a.m. - 9 a.m.	400	0.08	0.14			
	9 a.m. - 12 N.	180	0.09	0.13			
	12:15 p.m.	2.10	0.5 gm. uric acid intravenously
	12 N. - 4 p.m.	1,180	0.31	0.31	2.80	
5-6	4:15 p.m.		
	4 p.m. - 12 N.	1,585	0.65	1.05			
6	12 N. - 12 N.	2,765	0.96	1.36	1.20	Total amount for 24 hours
	4:15 p.m.	1.20	
6-7	12 N. - 12 N.	2,505	0.93	1.60			
-7	4:15 p.m.	1.70	1.70	
7-8	12 N. - 12 N.	3,016	0.87	1.88			
	4:15 p.m.	42.00	2.50	
8-9	1,380	0.49	1.11			
9	4:15 p.m.	1.6	

Endogenous output of uric acid November 2 to 5=2.74 gm.

Endogenous output of uric acid per day=0.69 gm.

Exogenous output of uric acid November 6 to 8=0.69 gm.

Per cent. of injected uric acid excreted=138 per cent.

Uric acid determinations were made by the original method.

CASE 3.—M. K., Med. No. 5708. White, female, aged 73.

Diagnosis: Psychoneurosis.

The patient was not an alcoholic. The physical examination was negative except for evidences of arteriosclerosis usual for the age. Blood pressure was 130 mm. systolic and 65 diastolic. The urine contained the slightest possible trace of albumin with the heat and nitric acid tests, and enough pus to render it turbid in appearance. Phthalein excretion was 55 per cent. in two hours. The patient was placed on a purin-free diet on Oct. 29, 1915.

Date	Time of Collection	Urine			Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Oct. 31 - Nov. 1	7 a.m. - 7 a.m.	2,035	0.32	0.59			
1-2	7 a.m. - 7 a.m.	1,130	0.29	0.54			
2-3	7 a.m. - 7 a.m.	1,384	0.36				
3-4	7 a.m. - 7 a.m.	1,048	0.21	0.53			
4	7 a.m. - 10 a.m.	250	0.05				
	10 a.m. - 12 N.	264	0.06				
	12 N.	0.8	
	12 N.	
	12 N. - 4 p.m.	167	0.01				
	4 p.m.	2.9	0.5 gm. uric acid intravenously
4-5	4 p.m. - 7 a.m.	920	0.32				
5	7 a.m. - 12 N.	340	0.19				
4-5	12 N. - 12 N.	1,427	0.52	0.54			
5	4 p.m.	1.4	
5-6	12 N. - 12 N.	1,590	0.40	0.57			
6	4 p.m.	39.2	0.8	
6-7	12 N. - 12 N.	1,820	0.33	0.61			
7-8	12 N. - 12 N.	1,350	0.32	0.56			

Endogenous output of uric acid November 1 to 4=1.18 gm.

Endogenous output of uric acid per day=0.30 gm.

Exogenous output of uric acid November 5 to 6=0.32 gm.

Per cent. of injected uric acid excreted=64 per cent.

Uric acid determinations were made by the original method.

CASE 4.—M. T. Mc., Med. No. 3415. White, female, aged 39.

Diagnosis: Chronic arthritis.

The patient's habits were good. Except for the joint changes of a chronic arthritis, the physical examination was negative. Blood pressure was 103 mm. systolic and 85 mm. diastolic. The urine contained the slightest possible trace of albumin and a small amount of pus microscopically.

Date	Time of Collection	Urine			Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Sept. 16	Purin-free diet begun
28	32.20	2.4	
Oct. 5-6	7 a.m. - 7 a.m.	2,190	0.34	0.88			
6-7	2,810	0.28	0.99			0.5 gm. uric acid intravenously
7-8	1,820	0.30	1.05			
8-9	1,575	0.32	0.98			
9	7 a.m. - 10 a.m.	440	0.03				
	1:20 p.m.	3.3	
	1:30 p.m.	
	10 a.m. - 12 N.	460	0.02	0.08			Total for 24 hrs.
	12 N. - 4 p.m.	440	0.10	0.17			
	6 p.m.	4.1	
9-10	4 p.m. - 7 a.m.	1,050	0.26	0.53			Total for 24 hrs.
10	2 p.m.	3.9	
9-10	12 N. - 12 N.	2,390	0.42	0.70	
10-11	7 - 7 a.m.	1,060	0.30	0.84			
11	2 p.m.	2.8	
11-12	1,715	0.33	0.89			
12	2.9	

Endogenous output of uric acid October 6 to 9=1.24 gm.

Endogenous output of uric acid per day=0.31 gm.

Exogenous output of uric acid October 10=0.11 gm.

Per cent. of injected uric acid excreted=22 per cent.

Uric acid determinations were made by the original method.

CASE 5.—W. H. K. Med. No. 5278. White, female, aged 29.

Diagnosis: Chronic arthritis.

The patient's habits were good. She had had chronic polyarthritis with occasional fairly acute exacerbations for the previous two years. The joints had never been either severely painful or tender. During the previous six months stiffness of the knees had prevented walking. Physical examination was negative except for the joints. There was limitation of motion and crepitation in all joints of the extremities. The elbows, wrists, finger joints, knees, and joints of both halluces were enlarged, principally as the result of thickening of the periarticular tissues. Blood pressure was 110 mm. systolic and 75 mm. diastolic. Urine examinations were negative except for a scant trace of albumin and a rare cast in one of the specimens. Phthalein excretion was 65 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Nonprotein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Oct. 31	1.8	Purin-free diet begun
Nov. 4-5	7 a.m. - 7 p.m.	830	0.57			
5-6	850	0.63			
6-7	740	0.56			
7-8	830	0.47			0.5 gm. uric acid intravenously
8	7 a.m. - 10 a.m.	350	0.01			
	10 - 12 N.	100	0.06			
	12 N.	1.6	
	12:15 p.m.	
	12 N. - 2 p.m.	297	0.18			
	2 - 5 p.m.	205	0.18			
	4:15 p.m.	2.5	
8-9	5 p.m. - 7 a.m.	297	0.19			
8-9	7 a.m. - 7 p.m.	1,249	0.57			
9	7 a.m. - 12 N.	278	0.16			
	12:15 p.m.	27.9	1.5	
8-9	12 N. - 12 N.	1,177	0.66			
9-10	7 a.m. - 7 a.m.	888	0.41			
10-11	7 a.m. - 7 a.m.	1,210	0.55			
11-12	1,045	0.75			
12-13	975	0.57			
13-14	1,170	0.61			

The daily output of uric acid was too variable to permit an accurate determination of an average endogenous level.

Endogenous output of uric acid November 5 to 8 = 2.23 gm.

Endogenous output of uric acid per day = 0.56 gm.

Exogenous output of uric acid November 9 = 0.10 gm.

Exogenous output of uric acid November 12 = 0.19 gm.

Per cent. of injected uric acid excreted November 9 = 20 per cent.

Per cent. of injected uric acid excreted November 12 = 38 per cent.

Total per cent. of injected uric acid excreted = 58 per cent.

Uric acid determinations were made by the uric acid phenol reagent method.

A study of the foregoing protocols shows a bizarre behavior in the output of the injected uric acid. Case 2 is the only one in which it is definitely apparent that the output of the exogenous uric acid began within the first four hours after its injection. The output began within the first twenty-four hours in Case 2, 3, 4 and 5. The excretion of the injected uric acid did not begin until during the second twenty-four-hour period after its administration in Case 1. In Case 5 the output of uric acid occurred in the first and fourth days following the injection. The excretion of the intravenously introduced uric acid was completed in from one to four days in all the above cases. In Case 1 determinations were stopped before the endogenous level in the urine had been reached. Thus there were great variations found both in the time of beginning and the duration of excretion of the injected uric acid.

The quantities of the intravenously injected uric acid which were excreted varied from 22 per cent. to 138 per cent. in the five cases. That a patient should excrete less than 100 per cent. of the amount of uric acid injected is explained by a loss occurring during the distribution throughout the body. Such a distribution must be necessarily undergone before the uric acid can reach the kidneys. As will be discussed later, other substances disappear from the blood after their intravenous injection. The output of more than 100 per cent. of the uric acid injected is only apparent. This is probably due to the variations commonly found in the daily endogenous amount of uric acid excreted. If the endogenous excretion has been low prior to the injection, and for the first few days following intravenous administration a higher endogenous output in the urine should be present, then the addition of a considerable amount of exogenous uric acid derived from that injected would make an apparent excretion of more than 100 per cent. It is to be noted that 0.1 gm. represents 20 per cent. of the amount of uric acid which was injected.

Our findings in the urine after the intravenous injection of uric acid into persons without gout show: (1) that the excretion may occur at irregular intervals; (2) that the starting of the excretion usually varies from a few hours to twenty-four hours; (3) that the percentage excreted ranges from very little to very much; and (4) that the duration of the output of injected uric acid is often protracted over several days.

The quantities of uric acid found in the blood after its intravenous injection varied in the different cases. In Case 1 no increase in the blood uric acid followed the injection. There was considerable fluctuation in the amounts present in this case. An increase in the blood uric acid was found four hours after the injection in Cases 2, 3, 4 and 5. This increase disappeared within the first twenty-four hours in Cases 2

and 5, but not until the second twenty-four hours after the injection in Cases 3 and 4.

Definite time relations between the disappearance of uric acid from the blood and its excretion in the urine cannot be established for non-gouty individuals from a study of the tables showing our results.

Intravenous Injections of Uric Acid into Gouty Persons.—Prior to our investigations, Umber and Retzlaff²⁷ had studied the output of intravenously injected uric acid in four patients with gout. In three the kidneys were stated to be normal. The percentages of uric acid excreted by these three patients were none, 8.6 per cent. and 24 per cent. within from one to two days. In their fourth case of gout the patient had "beginning albuminuria." In this case 23.6 per cent. of the injected uric acid was excreted within the first twenty-four hours. The results of this test in four cases have been published by Bürger and Schweriner.²⁸ One retained all the uric acid. The urine of this patient was free from albumin and casts. In the other cases small amounts were excreted. The urine of only one of these patients contained albumin and casts.

We have given four patients with gout intravenous injections of 0.5 gm. of uric acid. One patient had a severe type of nephritis. Of the others one showed no signs of nephritis and two such slight symptoms of that disease that kidney lesions could not be definitely diagnosed. The condition of the kidneys in these cases will be discussed in another communication on the study of the renal function in gout. The findings in the blood and urine after the uric acid injections are given in the following protocols.

27. Umber and Retzlaff: Zur Harnsäure-Retention bei der Gicht. Verhandl. d. Kong. f. inn. Med., Wiesbaden, 1910, **27**, 436.

28. Bürger, M., and Schweriner, F.: Ueber das Verhalten intravenös eingegebenen Glykoksäure bei gesunden und kranken Menschen (mit besonderer Berücksichtigung der Gicht und Lebercirrhose). Arch. f. exper. Pathol. u. Pharmacol., 1913, **74**, 353.

CASE 6.—D. J. T., Med. No. 2963. White, male, aged 55.

Diagnosis: Acute and chronic gout; arteriosclerosis; chronic nephritis; hypertension; chronic myocarditis; angina pectoris.

The patient had used one pint of rum a day for many years. He had had five attacks of typical podagra in the metatarsophalangeal joint of the right hallux during the previous fifteen years. One attack occurred while he was under observation in the hospital. Physical examination showed that the heart was enlarged to the left. The radial artery walls were tortuous and sclerotic. Blood pressure was 184 mm. systolic and 140 mm. diastolic. The urine contained a trace of albumin and an occasional cast. Phthalein excretion was 5 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Uric Acid in Mg. per 100 C.c.	Nonprotein N in Mg. per 100 C.c.	
1915 June 26	3.5	68.6	Purin-free diet begun
July 1-2	7 a.m. - 7 p.m.	550	0.07			
2-3	590	0.07			
3-4	620	0.10			
4-5	435	0.13			
5-6	1,060	0.33			
6-7	985	0.33			
7-8	1,010	0.33			
8-9	760	0.33			
9-10	710	0.25			
10-11	890	0.27			
11-12	570	0.20			
12-13	865	0.27			
13	1 p.m.	3.1		0.5 gm. uric acid intravenously
	1 p.m.		
	5 p.m.	4.9		
13-14	7 a.m. - 7 a.m.	950	0.47			
14	11 a.m.	4.1		
14-15	7 a.m. - 7 a.m.	935	0.35			
15	11 a.m.	4.7		
15-16	7 a.m. - 7 a.m.	660	0.17			
16	11 a.m.	2.9		
16-17	7 a.m. - 7 a.m.	923	0.35			
17-18	7 a.m. - 7 a.m.	994	0.34			

Endogenous output of uric acid July 5 to 13 = 2.36 gm.
 Endogenous output of uric acid per day = 0.30 gm.
 Exogenous output of uric acid July 14 to 15 = 0.22 gm.
 Per cent. of injected uric acid excreted = 44 per cent.
 Uric acid determinations were made by the original method.

CASE 7.—W. P. G., Med. No. 5471. Negro, male, aged 43.

Diagnosis: Gout; questionable chronic nephritis.

The patient's habits were good. During the last ten years he had had a dozen attacks of gout affecting the joints of the lower extremities and of the phalanges of the fingers. On physical examination numerous tophi were found in the ears and about the finger joints. Otherwise physical examination was negative. The blood pressure was 135 mm. systolic and 95 diastolic. The urine contained no casts, no blood and no epithelium. A scant trace of albumin was found once in the examination of several urine specimens. Phthalein excretion was 42 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Uric Acid in Mg. per 100 C.c.	Nonprotein N in Mg. per 100 C.c.	
1916 Oct. 21-22	7 a.m. - 7 a.m.	1,300	0.57	Purin-free diet begun
22-23	1,165	0.52			
23	3.3	43.5	
23-24	730	0.37			
24-25	705	0.41			
25-26	880	0.41			
26-27	990	0.37			
27	7 a.m. - 10 a.m. 10 a.m. - 12 N. 12 N. 12:15 p.m. 12 - 2 p.m. 4 p.m. 2 - 5 p.m.	115 90 95 180	0.05 0.03 0.04 0.07	4.1 5.1	Intravenously 0.5 gm. uric acid
27-28	5 p.m. - 7 a.m.	430 910	0.21 0.44	
28	4:15 p.m.	4.3		Total amount for 24 hours
28-29	7 a.m. - 7 a.m.	905	0.41			
29-30	625	0.28			
30-31	840	0.39			
31-Nov. 1	1,030	0.59			
1	
1-2	890	0.62	
2-3	1,350	0.59			Mild attack of gout Mild attack of gout
3-4	1,030	0.51			
4-5	1,035	0.53			
9	4.3	49.5	

Endogenous output of uric acid October 24 to 27 = 1.56 gm.

Endogenous output of uric acid per day = 0.39 gm.

Exogenous output of uric acid October 28 to 29 = 0.07 gm.

Per cent. of injected uric acid excreted = 14 per cent.

Uric acid determinations were made by the uric acid phenol reagent method.

CASE 8.—J. G., Med. No. 5421. White, male, aged 43.

Diagnosis: Gout; arteriosclerosis; hypertension; chronic myocarditis; very questionable chronic nephritis.

The patient had used beer freely. He had about sixteen attacks of severe polyarthrits of gouty character during the previous twenty-six years. Physical examination showed numerous tophi in the ears and on the fingers. The joints showed the changes of chronic arthritis. The radial artery walls were sclerosed. The blood pressure was 185 mm. systolic and 117 mm. diastolic. Otherwise physical examination was negative. The urine examinations were negative. Phthalein excretion was 52 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Uric Acid in Mg. per 100 C.c.	Nonprotein N in Mg. per 100 C.c.	
1916						
Oct. 10	6.4	Mixed diet
11	Purin-free diet begun
13	Acute attack of gout
15-16	7 a.m. - 7 a.m.	1,005	1.00	Acute attack of gout
16-17	960	1.01	Acute attack of gout
17	5.4	Acute attack of gout
17-18	1,260	0.71	Acute attack of gout
18-19	1,230	0.96	Acute attack of gout
19-20	Lost	Acute attack of gout
20-21	930	0.89	Acute attack of gout
21-22	905	0.68	Acute attack of gout
22-23	1,370	0.78	Acute attack of gout
23-24	1,355	0.80			
24-25	870	0.44			
25-26	830	0.70	Attack subsided
26-27	870	0.69			
27-28	840	0.71			
28-29	700	0.47			
29-30	670	0.41			
30	12 N.	4.1		
	12:15	0.5 gm. uric acid intravenously
	7 a.m. - 10 a.m.	105	0.08			
	10 a.m. - 12 N.	74	0.05			
	12 N. - 2 p.m.	171	0.11			
	2 - 5 p.m.	106	0.08	
	4:15 p.m.	4.6		
30-31	5 p.m. - 7 a.m.	330	0.22	Total amount for 24 hours
		786	0.52	
31	12:15 p.m.	4.8		
Oct. 31-						
Nov. 1	7 a.m. - 7 a.m.	820	0.51			
1-2	930	0.49			
2-3	950	0.63			
3-4	750	0.61			
4-5	670	0.46			
6	4.0	33.4	
Dec. 7	4.3	39.0	

The daily output of uric acid was too variable to permit an accurate determination of an average endogenous level.

Endogenous output of uric acid October 21 to 30 = 6.57 gm.

Endogenous output of uric acid per day = 0.66 gm.

Exogenous output of uric acid October 31 to November 5 = 0.

Uric acid determinations were made by the uric acid phenol reagent method.

CASE 9.—A. L. E., Med. No. 5297. White, male, aged 48.

Diagnosis: Gout; cirrhosis of the liver; questionable nephritis.

The patient had used large quantities of beer and whisky for many years. In the previous five years the patient had had five attacks resembling more the exacerbations of a chronic arthritis than gout. Three of these attacks occurred in the Peter Bent Brigham Hospital. Physical examination showed several tophi in the ears. The joints of the hands showed some periarticular thickening. The radial arteries were palpable. Blood pressure was 156 mm. systolic and 96 mm. diastolic. The liver edge was palpable 4 cm. below the right costal margin. Otherwise the physical examination was negative. The urine showed occasionally a scant trace of albumin and a few casts. Phthalein excretion was 24 per cent. in two hours.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Uric Acid in Mg. per 100 C.c.	Nonprotein N in Mg. per 100 C.c.	
Oct. 14	Purin-free diet begun
15	4.6	Acute gout
16-17	7 a.m. - 7 a.m.	850	0.94	Acute gout
17-18	750	0.93	Acute gout
18-19	550	0.55	Acute gout
19-20	Lost				
20-21	590	0.48	Mild acute gout
21-22	489	0.44	Mild acute gout
22-23	630	0.51	Mild acute gout
23-24	430	0.33	Mild acute gout
24-25	870	0.36	Mild acute gout
25-26	785	0.52	Mild acute gout
26-27	1,040	0.54	Mild acute gout
27-28	1,100	0.78	Mild acute gout
28-29	720	0.38	Mild acute gout
29-30	785	0.49	Mild acute gout
30-31	525	0.35	Mild acute gout
31-Nov. 1	785	0.52	Mild acute gout
1-2	710	0.44			
2-3	475	0.35			
3	7 a.m. - 10 a.m.	42	0.04			
	10 a.m. - 12 N.	67	0.05			
	12 N.	3.5		
	12:15 p.m.	0.5 gm. uric acid intravenously
	12 N. - 2 p.m.	31	0.03			
	2 - 5 p.m.	57	0.06			
	4:15 p.m.	5.7		
3-4	5 p.m. - 7 a.m.	219	0.18			
		416	0.37	Total amount for 24 hours
4	5.1	52.6	
4-5	7 a.m. - 7 a.m.	218	0.20	Questionable loss of one voiding of urine
5-6	550	0.40			
6-7	355	0.19			
7-8	400	0.28			
8-9	480	0.32			
9-10	460	0.29			
10-11	485	0.29			
14	4.1		

The daily output of uric acid was too variable to permit an accurate determination of an average endogenous level.

Endogenous output of uric acid October 21 to November 3 = 6.42 gm.

Endogenous output of uric acid per day = 0.46 gm.

Exogenous output of uric acid November 4 to 11 = 0.

Uric acid determinations were made by the uric acid phenol reagent method.

A study of the foregoing protocols shows that in Case 6, of nephritis, 44 per cent. of the injected uric acid was excreted. It will be noted that from July 2 to 4 the daily excretion of uric acid in this case was less than 0.1 gm., while a few days later it had risen to more than 0.3 gm. Case 7, without evidences of nephritis, put out 14 per cent. of the uric acid injected. In Cases 8 and 9 the daily excretion of uric acid was too variable to permit the calculation of an average endogenous level with accuracy. There was, however, no apparent rise above the endogenous output after the intravenous injections. There is a question as to whether one voiding of urine was lost the second night following the uric acid injection in Case 9. The variability in the endogenous excretion of uric acid in these two cases, 8 and 9, is connected with the gouty attacks which occurred during the periods of observation. Comparable findings were obtained in another case of gout with tophi, not included here, in which we studied the uric acid excretion during an acute attack. A very mild gouty attack occurred the night of the sixth day following the injection of uric acid in Case 7. These findings confirm the observation of Brugsch and Schittenhelm²⁹ who reported that in the same cases of gout there were periods of low and periods of high endogenous uric acid excretion.

A study of the tables shows that the amounts of uric acid³⁰ found in the blood in different cases of gout while on a purin-free diet varied from 3.1 to 4.1 mg. per 100 c.c. Higher values than these were present in Cases 8 and 9 during acute attacks and at a time when the patient, Case 8, was receiving a mixed diet. An increase in the blood under these two conditions has been pointed out by one of us.³¹ In all of the cases a rise of from 0.5 to 1.8 mg. of uric acid was present in the blood four hours after the intravenous injection of uric acid. This increase in blood uric acid persisted for forty-eight hours or longer in three of the cases (6, 8 and 9). In the remaining case (7) it disappeared within the first twenty-four hours. Three of these patients with gout retained the increase of uric acid in the blood twenty-four hours longer after the injection than did any of the nongouty patients.

Summary of the Results Obtained by the Intravenous Injections of Uric Acid.—Nine patients, five without gout and four with gout, have been given 0.5 gm. of uric acid intravenously. Determinations of the amounts of uric acid in the blood have shown a small but definite increase four hours after the injections in eight of the patients. From these findings it would seem highly probable that by the methods

29. Brugsch, T., and Schittenhelm, A.: Zur Stoffwechselfathologie der Gicht III Mittheilung. Ztschr. f. exper. Path. u. Therap., 1907, 4, 480.

30. By uric acid in the blood we mean the substance determined by the colorimetric method of Folin and Denis.

31. Pratt, J. H.: Studies on the Uric Acid in the Blood in Gout. Am. Jour. Med. Sc., 1916, 151, 92.

employed the substance quantitated in the blood after the intravenous injections was really uric acid. The increase in blood uric acid resulting after injection of uric acid disappeared within forty-eight hours after the injection in four nongouty and one of the gouty patients (Case 7). In the remaining three cases of gout it still persisted at the end of forty-eight hours.

The five nongouty patients excreted from 22 per cent. to 138 per cent. of the uric acid injected. Of the four cases of gout the one with nephritis put out 44 per cent. of the uric acid injected, while very little or none was excreted by the other three. These findings show that the failure to excrete a large percentage of uric acid after uric acid injections (exogenous uric acid) is not a pathognomonic symptom of gout, although it would seem to occur more frequently in gouty than in nongouty persons.

We have followed the method adopted by previous writers in computing the output of exogenous uric acid, to make our findings comparable with theirs. The method has been to determine the average daily endogenous uric acid excretion prior to the administration of purin-containing substances. After the injection or feeding of purin-containing materials all outputs in excess of the previously determined average endogenous output have been considered as exogenous uric acid.

This generally accepted method of calculation is often open to criticism. The daily outputs of endogenous uric acid are somewhat variable. It would probably be more correct to consider as exogenous uric acid only those outputs whose amounts are in excess of the maxi-

TABLE 4.—RESULTS OBTAINED BY THE TWO METHODS OF CALCULATING EXOGENOUS URIC ACID OUTPUT

Case	Average Daily Endogenous Output of Uric Acid in Gm.	Exogenous Uric Acid Output		Maximum Daily Output of Endogenous Uric Acid in Gm.	Exogenous Output of Uric Acid Exceeding Maximum Daily Endogenous Output	
		Gm.	Per Cent.		Gm.	Per Cent.
1	0.54	0.41	82	0.61	0.20	40
2	0.69	0.69	138	0.78	0.42	84
3	0.30	0.32	64	0.36	0.20	40
4	0.31	0.11	22	0.34	0.08	16
5	0.56	0.29	58	0.63	0.15	30
6	0.30	0.22	44	0.38	0.09	18
7	0.39	0.07	14	0.41	0.03	6
8	0.66	0	0	0.89	0	0
9	0.46	0	0	0.78	0	0

imum endogenous output. Otherwise one cannot be sure that a certain amount of what is really endogenous uric acid has not been included in the portion computed as exogenous uric acid. We have calculated the exogenous output after the intravenous injections of uric acid in our cases on this basis and the results are given in Table 4. For purposes of comparison the exogenous outputs as determined by the generally accepted method are also given.

Considering as exogenous uric acid only those outputs which exceeded the maximum endogenous excretion gives lower figures for the percentages of uric acid excreted. By this method of calculation the anomalous exogenous excretion of 138 per cent. in Case 2 drops to the reasonable figure of 84 per cent. The excretion of 44 per cent. of exogenous uric acid by gout Case 6 becomes 18 per cent. by this method of calculation, which is a more reasonable amount in a case of gout with nephritis of severe type.

III. EXOGENOUS URIC ACID EXCRETION AFTER THE FEEDING OF PURIN OR NUCLEIN CONTAINING SUBSTANCES

We have studied the exogenous uric acid excretion after feeding sweetbreads to a patient with chronic arthritis and to two with gout. Previous observers have employed the results obtained by studies on the excretion of exogenous uric acid (1) as a basis for theories relating to the etiology of gout, and (2) as an aid in the diagnosis of that disease. It is generally accepted that gouty patients eliminate less exogenous uric acid than do normal persons. But whether or not this phenomenon is of diagnostic importance is not well established. Certainly there is much controversy regarding the rôle of uric acid in the etiology of gout.

For purposes of comparison we have tabulated from the literature figures for the output of exogenous uric acid derived from the feeding of purin or nuclein containing substances to normal persons, to patients with chronic arthritis, and to patients with gout. In all of the tables exogenous uric acid will be expressed as the percentage of purin nitrogen in the substances fed which was excreted as uric acid nitrogen. In making the tabulations figures given by the observers quoted have been subjected to certain changes. In expressing the amounts of uric acid and of purin nitrogen, numerals beyond the second decimal place have been dropped. No decimals have been used in expressing the percentages of purin nitrogen excreted as uric acid nitrogen. We have supplied calculations wherever those requisite for our purposes had not been made by the author. Our additional calculations are designated in the tables by an asterisk. Observations have been collected only in which the experimental subjects received a known amount of some purin or nuclein containing substance while on an otherwise purin-free diet. The findings for normal man are given in Table 5.

TABLE 5.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY NORMAL MAN ON A PURIN-FREE DIET

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Minkowski ³²	18	0.23	1.82*	40*	3*	3 gm. hypoxanthin in 1 day	1.24*
Krüger and Smith ³³	1	0.46	2.31	62	3	3 gm. hypoxanthin in 2 days	1.24
Ackroyd ³⁴	1a	0.46	0.19	21	2	0.75 gm. hypoxanthin in 1 day	0.31
	1b	0.46	0.60	65	4	0.75 gm. hypoxanthin in 1 day	0.31
	2	0.42	0.66	72	2	0.75 gm. hypoxanthin in 1 day	0.31
	3	0.35	0.36	39	3	0.75 gm. hypoxanthin in 1 day	0.31
Brugsch and Schittenhelm ³⁵	10	0.24	1.23	23	2	Sodium thymonucleinate 30 gm. in 3 days	1.86
	12	0.33	1.54	24	1	Sodium nucleinate from yeast, 30 gm. in 3 days	2.17
Pollak ³⁵	1	0.43	0.56	30	2	Sodium nucleinate 20 gm. in 1 day	0.79*
	2	0.42	0.45	38	2	10 gm. in 1 day	0.40*
	3	0.27	0.51	22	3	20 gm. in 1 day	0.79*
Mendel and Lyman ³⁶	W.W.H.	0.37	0.74	64	3	1.5 gm. hypoxanthin nitrate	0.39
	J.F.L.	0.38	0.66	57	3	1.5 gm. hypoxanthin nitrate	0.39
Plimmer, Dick, and Lieb ³⁷	..	0.43	0.12	..	1	13 gm. nucleic acid in 3 days	
Bloch ³⁸	1	0.49	0.94	48	2	10 gm. nucleic acid in 1 day	0.66
	2	0.50	0.83	42	3	10 gm. nucleic acid in 1 day	0.66
	3	0.33	1.03	52	2	10 gm. nucleic acid in 1 day	0.66
Mallory ³⁹	1	0.42	0.31	39	3	4 gm. nucleic acid in 1 day	0.26

* This figure represents our calculation made from the table given by the author quoted.

† The method of administration was per os in each instance.

32. Minkowski, O.: Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. f. exper. Path. u. Pharmacol., 1898, **41**, 375.

33. Krüger, M., and Schmid, J.: Die Entstehung der Harnsäure aus freien Purinbasen. Ztschr. f. Physiol. Chem., 1901-1902, **34**, 549.

34. Ackroyd, H.: Observations on Purin Metabolism. Bull. Com. for Study of Special Diseases, Edinburgh, 1907, **2**, 146.

35. Pollak, L.: Ueber Harnsäureausscheidung bei Gicht und Alkoholismus. Deutsch. Arch. f. klin. Med., 1907, **88**, 224.

36. Mendel, L. B., and Lyman, J. E.: A metabolism of Some Purin Compounds in the Rabbit, Dog, Pig, and Man. Jour. Biol. Chem., 1910-1911, **8**, 115.

37. Plimmer, R. H. A., Dick, M., and Lieb, C. C.: A Metabolism Experiment with Special Reference to the Origin of Uric Acid. Jour. Physiol., 1909-1910, **39**, 98.

38. Bloch, B.: Beiträge zur Kenntniss des Purinstoffwechsels beim Menschen. Deutsch. Arch. f. klin. Med., 1905, **83**, 499.

39. Mallory, W. J.: Observations on Uric Acid Excretion in Gout and Rheumatoid Arthritis. Bull. Com. for Study of Special Diseases, 1908-1909, **3**, 17.

TABLE 5.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY NORMAL MAN ON A PURIN-FREE DIET—(Continued)

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Morris ⁴⁰	1	0.38	0.17	22	2	4 gm. nucleic acid in 1 day	0.26
Krüger and Smith ⁴³	1a	0.46	0.15	41	2	0.3 gm. adenin in 1 day	
	1b	0.46	0.31	41	3	0.6 gm. adenin in 1 day	
Hirschstein ⁴¹ ...	4	0.36*	1.45*	11*	1	1,000 gm. thymus in 2 days	4.50*
Burian and Schur ⁴²	10	0.52	1.77	26	2	620 gm. thymus in 2 days	2.48
Ljungdahl ⁴³ ...	1	1.01	28	4	300 gm. thymus in 1 day	1.20
	2	1.37	38	5	300 gm. thymus in 1 day	1.20
	3	0.45	13	2	300 gm. thymus in 1 day	1.20
	4	0.87	24	2	300 gm. thymus in 1 day	1.20
	5	0.93	26	3	300 gm. thymus in 1 day	1.20
	6	1.17	33	3	300 gm. thymus in 1 day	1.20
Burian and Schur ⁴²	10	0.52	0.95	53	3	500 gm. liver in 1 day	0.6
	13	0.55	0.24	44	1	300 gm. ham in 1 day	0.18
	3	0.56	1.34*	74*	1	1,000 gm. beef in 4 days	0.6*
	5	0.39	0.52*	38*	1	760 gm. beef in 4 days	0.46*
Kaufmann and Mohr ⁴⁴	7	0.54*	2.71*	44*	2*	900 gm. veal in 4 days	0.54*
		0.54*	0.12*	8*	3*	900 gm. beef in 4 days	0.54*
	8	0.47*	0.53*	59*	2*	500 gm. beef in 3 days	0.30*
Plimmer, Dick and Lieb ³⁷	..	0.43*	2.77*	47*	3	3,500 gm. beef in 7 days	1.95*
Weiss ⁴⁵	1	0.36	0.51	46	3	750 gm. beef in 2 days	0.38
		0.36	1.01	53	3	1,250 gm. beef in 2 days	0.63
Walker Hall ⁴⁶ ..	14	0.43	0.21	29	1	400 gm. beef in 1 day	0.24

40. Morris, E. H.: Observations on the Uric Acid Excretion in One Normal Person, and in Four Cases of Rheumatoid Arthritis. Bull. Com. for Study of Special Diseases, Edinburgh, 1910, **3**, 57.

41. Hirschstein, L.: Die Beziehungen des Glykokolls zur Harnsäure. Ztschr. f. exper. Pathol. u. Therap., 1907, **4**, 118.

42. Burian, R., and Schur, H.: Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. Arch. f. d. gesamt. Physiol., 1900, **80**, 241.

43. Ljungdahl, M.: Ueber die Harnsäureausscheidung bei den chronischen nicht gichtischen Polyarthritiden und ihre Bedeutung für die Differentialdiagnose zwischen Gelenkerkrankungen gichtischer und nicht gichtischer Natur. Ztschr. f. klin. Med., 1913-1914, **79**, 177.

44. Kaufmann, M., and Mohr, L.: Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. Deutsch. Arch. f. klin. Med., 1902, **74**, 141 and 586.

45. Weiss, P.: Beiträge zur Wertbestimmung der Ausscheidung der endogenen und exogenen Harnsäure bei Gicht und anderen Erkrankungen. Ztschr. f. klin. Med., 1908, **66**, 131.

46. Hall, I. W.: The Purin Bodies of Foodsuffs. Manchester, 1902, p. 64.

Summary of Table 5.—In normal human beings after feeding hypoxanthin the percentage of purin nitrogen excreted as uric acid nitrogen varied from 21 per cent. to 72 per cent.; after feeding a nucleinate or nucleic acid, from 22 per cent. to 52 per cent.; after giving adenin it was 41 per cent.; after feeding thymus it varied from 11 per cent. to 38 per cent., and after beef, ham or veal, from 8 per cent. to 74 per cent. The mean average percentage of excretion of exogenous uric acid nitrogen after feeding the above named substances to normal individuals was 39 per cent., the extremes of excretion being 8 per cent. and 74 per cent. After feeding beef the exogenous uric acid varied from 8 per cent. to 44 per cent. in a person reported by Kaufmann and Mohr.⁴⁴ After administering hypoxanthin to a person reported by Ackroyd³⁴ the excretion of exogenous uric acid nitrogen was 21 per cent. after the first feeding and 65 per cent. after the second. Thus there is a considerable variation in the amount of exogenous uric acid both among different persons and in the same person.

The time required to complete the excretion of the exogenous uric acid varied from one to five days.

Table 6, showing the output of exogenous uric acid after feeding purin or nuclein containing substances to patients with chronic non-gouty arthritis, is for the most part taken from one compiled by Mallory.³⁰ All patients were on a purin-free diet.

TABLE 6.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY PATIENTS WITH CHRONIC ARTHRITIS WHO WERE ON A PURIN-FREE DIET

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Kaufmann and Mohr ⁴⁴	44	0.43	2.47	8	5	2,500 gm. thymus in 5 days	10
	45	0.47	2.33	13	3	1,500 gm. thymus in 3 days	6*
Ackroyd ³⁴	4a	0.26	0.59	64	3	0.75 gm. hypoxanthin in 1 day	0.31
	4b	0.26	0.46	50	2	0.75 gm. hypoxanthin in 1 day	0.31
	5	0.33	0.44	49	3	0.75 gm. hypoxanthin in 1 day	0.31
	6	0.32	0.57	61	3	0.75 gm. hypoxanthin in 1 day	0.31
	7	0.35	0.40	43	2	0.75 gm. hypoxanthin in 1 day	0.31
	8	0.33	0.21	34	3	0.5 gm. hypoxanthin in 1 day	0.21
	9	0.32	0.92	99	6	0.75 gm. hypoxanthin in 1 day	0.31
	10	0.34	0.53	87	7	0.5 gm. hypoxanthin in 1 day	0.21
	11	0.53	0.61	100	7	0.5 gm. hypoxanthin in 1 day	0.21
	12	0.49	0.31	33	6	0.75 gm. hypoxanthin in 1 day	0.31
	14	0.34	0.41	44	9	0.75 gm. hypoxanthin in 1 day	0.31

* This figure represents our calculation made from the table given by the author quoted.
† The method of administration was per os in each instance.

TABLE 6.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY PATIENTS WITH CHRONIC ARTHRITIS WHO WERE ON A PURIN-FREE DIET—(Continued)

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Mallory ³⁰	1b	0.35	0.14	15	2	0.75 gm. hypoxanthin in 1 day	0.31
	2b	0.30	0.24	25	4	0.75 gm. hypoxanthin in 1 day	0.31
	c	0.30	0.33	35	3	0.75 gm. hypoxanthin in 1 day	0.31
	d	0.30	0.25	27	3	0.75 gm. hypoxanthin in 1 day	0.31
	3b	0.30	0.50	53	2	0.75 gm. hypoxanthin in 1 day	0.31
	5b	0.30	0.55	59	4	0.75 gm. hypoxanthin in 1 day	0.31
	6b	0.31	0.33	41	3	0.75 gm. hypoxanthin in 1 day	0.31
Morris ⁴⁰	2b	0.21	0.25	27	3	0.75 gm. hypoxanthin in 1 day	0.31
	3b	0.20	0.40	43	3	0.75 gm. hypoxanthin in 1 day	0.31
Mallory ³⁰	1a	0.35	0.06	7	3	4 gm. nucleic acid in 1 day	0.26
	2a	0.30	0.24	31	2	4 gm. nucleic acid in 1 day	0.26
	3a	0.30	0.26	32	2	4 gm. nucleic acid in 1 day	0.26
	4	0.39	0.36	46	3	4 gm. nucleic acid in 1 day	0.26
	5a	0.30	0.63	80	8	4 gm. nucleic acid in 1 day	0.26
	6a	0.31	0.76	97	6	4 gm. nucleic acid in 1 day	0.26
Morris ⁴⁰	2a	0.21	0.14	18	4	4 gm. nucleic acid in 1 day	0.26
	3a	0.20	0.14	18	3	4 gm. nucleic acid in 1 day	0.26
	4	0.31	0.81	103	7	4 gm. nucleic acid in 1 day	0.26
Ljungdahl ⁴³	1	0.95	26	2	300 gm. thymus	1.20
	2	0.54	15	2	300 gm. thymus	1.20
	3	0.39	11	2	300 gm. thymus	1.20
	4	0.46	19	2	200 gm. thymus	0.80
	5	0.60	19	2	300 gm. thymus	1.20
	6	1.15	48	7	200 gm. thymus	0.80
	7	1.20	33	7	300 gm. thymus	1.20
	8	0.50	14	2	300 gm. thymus	1.20
	9	0.95	26	5	300 gm. thymus	1.20
	10	0.28	8	1	300 gm. thymus	1.20
	11	0.24	7	1	300 gm. thymus	1.20
	12	1.12	31	6	300 gm. thymus	1.20
Hösslin and Kato ⁴⁷	1	0.28*	1.41*	60*	5*	10 gm. sodium nucleinate	0.66*
	4	0.30*	0.12*	6*	2*	10 gm. sodium nucleinate	0.66*
	5	0.35*	2.30*	80*	5*	15 gm. sodium nucleinate	0.99*
	6	0.33*	0.70*	24*	3*	15 gm. sodium nucleinate	0.99*
	8	0.35*	0.14*	7*	1*	10 gm. sodium nucleinate	0.99*
	10	0.29*	0.20*	6*	1*	15 gm. sodium nucleinate	0.99*
	11	0.34*	0.02*	1*	1*	15 gm. sodium nucleinate	0.99*
	12	0.42*	0.89*	31*	4*	15 gm. sodium nucleinate	0.99*

47. von Hösslin, H., and Kato, K.: Ueber Harnsäureausscheidung bei Gicht und Gelenkrheumatismus. Deutsch. Arch. f. klin. Med., 1910, 99, 301.

Summary of Table 6.—In patients with chronic nongouty arthritis the percentage of purin nitrogen excreted as uric acid nitrogen after feeding hypoxanthin ranged from 15 per cent. to 99 per cent., after giving nucleic acid from 77 per cent. to 103 per cent., after sodium nucleinate from 1 per cent. to 80 per cent., and after thymus from 8 per cent. to 48 per cent. The mean average excretion of all these substances was 38 per cent. After feeding hypoxanthin the exogenous uric acid excretion varied from 50 per cent. to 64 per cent. in one of Ackroyd's³⁴ cases, and from 25 per cent. to 35 per cent. in one reported by Mallory.³⁰ The table shows that there is great variation in the amount of exogenous uric acid excreted by the different patients. This was also found in normal persons (Table 5). The time required to excrete the exogenous uric acid varied from one to nine days.

The cases reported by Kaufmann and Mohr,⁴⁴ Ackroyd,³⁴ Mallory³⁰ and Morris⁴⁰ were without evidences of nephritis. It is inferred from the text in the reports of Ljungdahl⁴³ and of Hösslin and Kato⁴⁷ that the patients were not nephritics.

We have studied the excretion of uric acid after a meal of sweetbreads in a patient with chronic polyarthritis. There were no evidences of kidney disease or of gout in this patient. The findings are given in Table 7.

TABLE 7.—EXOGENOUS URIC ACID EXCRETION IN CHRONIC ARTHRITIS

(W. H. K. Med. No. 5278. Diagnosis: Chronic arthritis. For notes on this patient see Case 5.)

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Nonprotein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
Oct. 31	Purin-free diet begun
Nov. 9.	27.9	1.5	
16-17	7 a.m. - 7 a.m.	1,480	0.44			
17-18	1,010	0.39			
18-19	845	0.38			
19-20	1,235	0.37			Patient given 184 gm. sweetbreads
20-21	1,310	0.43			
21	1 p.m.	
	7 p.m.	2.6	
21-22	1 p.m. - 1 p.m.	7,429	0.93			
22	11 a.m.	1.5	
22-23	1 p.m. - 1 p.m.	1,490	0.53			
23-24	1 p.m. - 1 p.m.	925	0.49			
24-25	1 p.m. - 1 p.m.	905	0.33			

Endogenous output of uric acid November 17 to 21 = 2.01 gm.

Endogenous output of uric acid per day = 0.40 gm.

Exogenous output of uric acid November 22 to 24 = 0.75 gm.

Purin nitrogen in 184 gm. of sweetbreads calculated according to Burian and Schur = 0.83 gm.

Per cent. of purin nitrogen excreted = 30 per cent.

Uric acid determinations made by the uric acid reagent method.

Thirty per cent. of the purin nitrogen fed was excreted as uric acid nitrogen by our patient. These findings are comparable to those reported in the literature.

The exogenous uric acid excretion by gouty persons who were under the same experimental conditions as the normal and arthritic subjects in the foregoing tables is given in Table 8.

TABLE 8.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY GOUTY PERSONS ON A PURIN-FREE DIET

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Brugsch and Schittenhelm ²⁰	4	0.23	0.39	14	4	Sodium thymonucleinate, 20 gm. in 2 days	1.24
	5	0.33	0.57	15	5	Sodium thymonucleinate, 20 gm. in 2 days	1.24
	11	0.13	0.35	6	6	Sodium thymonucleinate, 30 gm. in 3 days	1.86
See Footnote 49	8	0.25	0.16	16	3	Sodium thymonucleinate, 5 gm. in 1 day	0.31
See Footnote 29	4	0.22	0.44	20	4	Yeast sodium nucleinate, 10 gm. in 1 day	0.72
		0.23	0.44	20	4	Yeast sodium nucleinate, 50 gm. in 5 days	3.61
	5	0.00	0	0	Yeast sodium nucleinate, 20 gm. in 2 days	1.44
	13	0.31	1.54	36	5	Yeast sodium nucleinate, 20 gm. in 2 days	1.44
						8 gm. thymonucleic acid in 1 day	
Neustadt ⁴⁸	K2	0.48	0.00	0	..	10 gm. nucleic acid in 1 day	
Pollak ³⁶	4	0.06	0.19	16	4	10 gm. nucleic acid in 1 day	0.40
	5	0.23	0.24	19	2	10 gm. nucleic acid in 1 day	0.40
	6	0.27	0.43	20	3	18 gm. nucleic acid in 1 day	0.71
Mallory ³⁹	9a	0.18	0.02	3	1	4 gm. nucleic acid in 1 day	0.26
	10a	0.31	0.02	3	1	4 gm. nucleic acid in 1 day	0.26
	11a	0.17	0.24	30	4	4 gm. nucleic acid in 1 day	0.26
Brugsch and Schittenhelm ⁴⁰	1	0.29	0.16	13	2	1 gm. hypoxanthin in 1 day	0.41
	2	0.29	0.15	12	1	1 gm. hypoxanthin in 1 day	0.41
Mallory ³⁹	9b	0.18	0.03	3	1	0.75 gm. hypoxanthin in 1 day	0.31
	10b	0.31	0.09	10	2	0.75 gm. hypoxanthin in 1 day	0.31
	11b	0.17	0.10	10	3	0.75 gm. hypoxanthin in 1 day	0.31

* This figure represents our calculation made from the table given by the author quoted.
† The method of administration was per os in each instance.

48. Neustadt, G.: Das Verhalten verfütterter Purinbasen bei der Gicht. Ztschr. f. exper. Path. u. Therap., 1911-1912, **10**, 296.

49. Brugsch, T., and Schittenhelm, A.: Zur Stoffwechselfathologie der Gicht. VIII Mittheil. Ztschr. f. exper. Path. u. Therap., 1908-1909, **5**, 215.

TABLE 8.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY GOUTY PERSONS ON A PURIN-FREE DIET—(Continued)

Observer	Observation Period	Daily Average Endogenous Output of Uric Acid in Gm.	Output of Exogenous Uric Acid in Gm.	Per Cent. of Purin Nitrogen Excreted as Uric Acid N	Number of Days of Exogenous Uric Acid Excretion	Substance Given	Purin Nitrogen in Substance Given†
Rotky ⁵⁰	3-2	0.34	0.07	11	3	0.5 gm. hypoxanthin in 1 day	0.21
Neustadt ⁴⁸	1.2	0.36	0.79	109	4	0.5 gm. hypoxanthin in 1 day	0.21
	K3	0.48	0.02	5	3	0.25 gm. hypoxanthin in 1 day	0.10
		0.45	0.38	61	3	0.5 gm. hypoxanthin in 1 day	0.21
		0.48	0.09	15	3	0.5 gm. hypoxanthin in 1 day	0.21
		0.51	0.42	69	4	0.5 gm. hypoxanthin in 1 day	0.21
Levine and Kristeller ⁵¹	1	0.24	0.15	20	4	7.5 gm. uric acid in 1 day	2.5
		0.24	0.00	0	0	7.5 gm. uric acid in 1 day	2.5
	2	0.23	1.14	5	6	24 gm. uric acid in 4 days	8.0
		0.23	0.86	2	2	24 gm. uric acid in 4 days	8.0
	1	0.23	0.23	3	4	Nucleic acid, 1 day	2.83
	2	0.23	1.50	6	4	Nucleic acid, 4 days	8.0
Neustadt ⁴⁸	1.6	0.41	0.21	38	3	0.35 gm. adenin in 1 day	0.18
Brugsch and Schittenbeim ⁴⁹	..	0.25	0.44	41	5	0.7 gm. adenin in 1 day	0.36
Kaufmann and Mohr ⁴⁴	39	0.46*	2.31*	22*	4*	800 gm. thymus in 4 days	3.60*
	40	0.50*	1.44*	12*	2*	900 gm. thymus in 2 days	4.05*
	41	0.49*	1.30*	8*	2*	1,200 gm. thymus in 4 days	5.40*
	42	0.40*	0.72*	5*	1*	900 gm. thymus in 3 days	4.05*
	46	0.32*	2.69*	22*	5+*	900 gm. thymus in 3 days	4.05*
Strauss ⁵²	0.41*	0.33*	8*	2	325 gm. thymus in 1 day	1.46*
Brugsch ⁵³	1	0.55*	0.00*	0.00*	0*	800 gm. thymus in 4 days	3.00*
Hirschstein ⁴¹ ...	5	0.06*	17*	9*	0+*	1,000 gm. thymus in 2 days	4.50*
Rotky ³⁴	3	0.34*	0.04	3	2	100 gm. thymus in 1 day	0.45*
Kaufmann and Mohr ⁴⁴	47	0.39	0.40	27*	1	800 gm. veal in 4 days	0.48*
		0.40	0.30	21*	1	800 gm. beef in 4 days	0.48*
Soetbeer ⁵⁴	3	0.42	0.12	25*	1+*	250 gm. beef in 1 day	0.15*
	4	0.50	0.08	10*	2+*	500 gm. beef in 1 day	0.30*
	5	0.30*	0.00*	0.00*	..	700 gm. beef in 2 days	0.18*
Brugsch ⁵³	0.55	0.00	0.00	..	800 gm. beef in 8 days	0.48*
Soetbeer ⁵⁴	2	0.28	0.92	57	3+*	900 gm. ham in 3 days	0.54*
Weiss ⁴⁵	0.29	0.42	37	8	750 gm. beef	0.38
Hall ⁵⁵	4	0.17*	0.22*	106	3	Beef extract	0.07

50. Rotký, H.: Beiträge zur Pathologie des Nukleinstoffwechsels. Deutsch. Arch. f. klin. Med., 1909-1910, **98**, 540.

51. Levene, P. A., and Kristeller, L.: Nitrogen and Nuclein Metabolism in Gout. Jour. exper. Med., 1912, **16**, 303.

52. Strauss, H.: Pathogenese und Therapie der Gicht. Würzburger Abhandl. a. d. Gesamt. d. prakt. Med., 1902, **2**, 209.

53. Brugsch, T.: Zur Stoffwechselfathologie der Gicht. Ztschr. f. exper. Path. u. Therap., 1905-1906, **2**, 619.

54. Soetbeer, F.: Ueber den Einfluss der Nahrungsaufnahme auf die Ausscheidung der Harnsäure bei Arthritis urica. Ztschr. f. physiol. Chem., 1903-1904, **40**, 25.

55. Hall, I. W.: The Chemical Pathology of Gout. Brit. Med. Jour., 1904, **2**, 744.

Summary of Table 8.—In gouty patients the percentage of purin base nitrogen excreted as uric acid nitrogen after feeding hypoxanthin varied from 5 per cent. to 109 per cent., after adenin it was 40 per cent., after giving nucleic acid it ranged from 3 per cent. to 30 per cent., after sodium nucleinate from none to 36 per cent., after thymus from none to 22 per cent., and after some form of beef or ham from none to 106 per cent. The mean average percentage of excretion as exogenous acid nitrogen of all these substances fed was 20 per cent.

It will be noted that the exogenous uric acid output in the patients whose urine contained albumin and casts was as great as in those in whom the urine was reported as normal.

We have studied the uric acid excretion in two cases of gout after feeding sweetbreads. The findings are given in Tables 9 and 10. The patient whose data are given in Table 8 has already been described as Case 9. The patient whose data appears in Table 9 was one who used alcoholic drinks to excess. During the previous nine years the patient had had six attacks of podagra in the right great toe joint. In the previous six years there had been several polyarticular attacks of arthritis, gouty in nature, which involved the joints of the hands, knees, toes and ankles. During the study of the patient's uric acid excretion an attack of gout occurred the day following the ingestion of 188 gm. of sweetbreads. The middle finger, dorsum of the hand and wrist were involved. On physical examination large tophi were found in the left ear, about the olecranon processes of both ulnae and on the plantar surfaces of both wrists, and on all the fingers. Sodium urate crystals were obtained from certain of the tophi. There were no evidences of cardiovascular disease. The blood pressure was 126 mm. systolic and 96 mm. diastolic. The urine contained neither albumin nor casts. The patient was put on a purin-free diet Oct. 8, 1916.

TABLE 9.—EXOGENOUS URIC ACID EXCRETION IN GOUT
(A. L. E., Med. No. 5297. Diagnosis: Gout.)

Date	Time of Collection	Urine		Blood		Remarks
		Amount in O.c.	Uric Acid in Gm.	Nonprotein N in Mg. per 100 O.c.	Uric Acid in Mg. per 100 O.c.	
1916 Nov. 1	Purin-free diet begun
20-21	7 a.m. - 7 a.m.	475	0.15			
21-22	Lost				
22-23	7 a.m. - 7 a.m.	695	0.14			
23-24	7 a.m. - 7 a.m.	460	0.10			
24-25	7 a.m. - 7 a.m.	715	0.13			
25	1 p.m.	54.3	4.5	Patient given 150 gm. sweetbreads
	1 p.m.	
	7 p.m.	5.8	
25-26	1 p.m. - 1 p.m.	725	0.19			
26	1 p.m.	5.1	
26-27	1 p.m. - 1 p.m.	895	0.19			
27-28	1 p.m. - 1 p.m.	785	0.13			
29	1 p.m.	4.8	

Endogenous output of uric acid November 21 to 25 = 0.52 gm.

Endogenous output of uric acid per day = 0.13 gm.

Exogenous output of uric acid November 26 to 27 = 0.12 gm.

Purin nitrogen in 150 gm. of sweetbreads calculated according to Burian and Schur = 0.68 gm.

Per cent. of exogenous purin nitrogen excreted = 6.

Uric acid determinations made by the uric acid reagent method.

TABLE 10.—EXOGENOUS URIC ACID EXCRETION IN GOUT
AFTER FEEDING SWEETBREADS

J. J. N. White, male, aged 35. Many tophi on hands and feet.
Diagnosis: Gout.

Date	Time of Collection	Urine		Blood, Uric Acid in Mg. per 100 C.c.	Remarks
		Amount in C.c.	Uric Acid in Gm		
1916 Oct. 7	Purin-free diet begun
12-13	7 a.m. - 7 a.m.	1,690	0.26		
13-14	7 a.m. - 7 a.m.	1,440	0.25		
14-15	7 a.m. - 7 a.m.	1,570	0.27		
15-16	7 a.m. - 7 a.m.	1,860	0.26		
16-17	7 a.m. - 7 a.m.	2,100	0.33		
17-18	7 a.m. - 7 a.m.	1,860	0.25		
18-19	7 a.m. - 7 a.m.	1,770	0.25		
19-20	7 a.m. - 7 a.m.	1,515	0.40		
20	12 noon	2.2	
20-21	7 a.m. - 7 a.m.	1,620	0.49	4.4	Acute attack of gout
21-22	7 a.m. - 7 a.m.	2,100	0.59	8.7	
22-23	7 a.m. - 7 a.m.	1,500	0.29	2.7	
23-24	7 a.m. - 7 a.m.	1,865	0.37		
24-25	7 a.m. - 7 a.m.	1,660	0.25	5.0	
Nov. 7	7.4	

Endogenous output of uric acid October 13 to 19=1.87 gm.

Endogenous output of uric acid per day=0.27 gm.

Exogenous uric acid excreted October 21 to 22=0.67 gm.

Purin nitrogen in 188 gm. of sweetbreads according to Burian and Schur=0.9 gm.

Percentage of purin nitrogen excreted as uric acid nitrogen=24.

Our patients with gout excreted 6 per cent. and 24 per cent. of the purin nitrogen contained in the sweetbreads in the form of uric acid nitrogen. These findings are comparable to those reported for gout cases in the literature.

The results obtained by a comparative study of exogenous uric acid excretion by normal, by arthritic, and by gouty persons are shown in Tables 11 and 12.

TABLE 11.—PERCENTAGE OF PURIN NITROGEN EXCRETED AS URIC ACID NITROGEN
AFTER FEEDING PURIN OR NUCLEIN CONTAINING SUBSTANCES

Diagnosis	Number of Cases	Total Number of Experi- ments	Number of Experiments and Percentages of Purin Nitrogen Excreted as Uric Acid Nitrogen			
			0-10	10-20	20-30	30-100
Normal.....	35	40	1	2	11	26
Chronic arthritis.....	41	52	8	9	7	28
Gout.....	32	50	19	13	7	11

Table 11 shows conclusively that the output of exogenous uric acid is usually smaller in gout than in either normal or arthritic persons.

Twenty-eight, or 87.9 per cent., of the gouty patients excreted as uric acid nitrogen less than 20 per cent. of the purin nitrogen ingested, while thirty-one, or 88.6 per cent., of normal persons and twenty-five, or 69.7 per cent., of nongouty, arthritic patients excreted more than 20 per cent. Regardless of the substances fed the average exogenous uric acid nitrogen excretion in gout was 20 per cent., while by the normal persons it was 39 per cent., and by arthritic patients 38 per cent. The small output of exogenous uric acid occurs frequently enough in gout to be considered as a symptom of that disease. But as a pathognomonic symptom of gout it is not of much importance, since it also occurs in 11.4 per cent. of normal persons, and in 30.3 per cent. of arthritic nongouty patients.

A prolonged excretion of exogenous uric acid has been considered as a symptom of gout. The duration in days of the output of exogenous uric acid has been compiled from Tables 5 to 10 and the results are given in Table 12.

TABLE 12.—DURATION IN DAYS OF EXOGENOUS URIC ACID EXCRETION AFTER FEEDING PURIN OR NUCLEIN CONTAINING SUBSTANCES

Diagnosis	Number of Cases	Total Number of Experiments	Number of Experiments with Duration in Days of Exogenous Uric Acid Excretion								
			1	2	3	4	5	6	7	8	9
Normal.....	35	40	6	15	16	2	1				
Chronic arthritis..	41	52	5	13	15	4	4	4	5	1	1
Gout.....	32	46	9	10	11	7	4	2	1	2	

All normal persons excreted the exogenous uric acid within five days. Of fifty-two experiments on arthritic patients, the exogenous uric acid output was completed within five days in forty-one, or 78.8 per cent., and of forty-six experiments on the gouty persons the output was completed within five days in forty-one, or 89.1 per cent. Therefore, a prolongation of the excretion of exogenous uric acid over that of the normal does not occur frequently enough in gout to be considered a symptom of that disease.

The striking fact brought out in the last two tables is the great variations in the percentage output of exogenous uric acid and in its duration. Either a delayed and diminished output is not evidence of disturbances in the intermediary metabolism of nucleins, or the intermediary metabolism of nucleins is easily deranged.

SUMMARY AND DISCUSSION

Our studies on the intravenous injection of uric acid and the feeding of nuclein containing material, together with the compilations we have made from reports in the literature, show that in normal and non-gouty as well as in gouty persons there is great variability in the quantity and in the duration of exogenous uric acid excretion. For this reason a diminished or a protracted exogenous uric acid output most probably results from factors other than disturbances in the nuclein intermediary metabolism. If this is not true, then derangements in nuclein metabolism are so common that their importance in the etiology of any diseased condition is problematic.

Umber⁵⁶ advanced the hypothesis that the failure of gouty persons to excrete exogenous uric acid was due to a special affinity of the tissues for uric acid. We have found that intravenously injected uric acid usually remains in the blood stream longer in gouty than in non-gouty persons. The reverse would have been expected if Umber's theory were correct.

By statistical evidence we have shown that in the majority of gouty persons the uric acid in the blood is more than 3 mg. per 100 c.c. when determined by the method of Folin and Denis. That the substance which has been determined was actually uric acid is made probable by the following considerations: (1) It is well known that in gout there is a deficient output of uric acid; this substance would then tend to accumulate in the blood; (2) less uric acid is found in the blood of persons without gout than of those with that disease. The conditions which form exceptions to this statement have already been enumerated, but their character is such that in the large majority retention of uric acid is readily explained; (3) following the intravenous injections of uric acid an increase in that substance occurs in the blood.

The fate of that part of intravenously injected uric acid which is not excreted within the first few days is unknown. In fact, this additional uric acid disappeared from the blood in all of our cases, except one, before its excretion began. Since uric acid is not known to be destroyed in the body, we offer the explanation that the excess which we injected went into the body tissues. Van Slyke⁵⁷ has shown that intravenously introduced amino-acids quickly disappear from the blood. He discovered that they were to be found in the muscles, where they were held either mechanically or in loose molecular combinations.

56. Umber, F.: *Ernährung und Stoffwechselkrankheiten*. Ed. 2, Berlin, 1914.

57. Van Slyke, D. D.: *The Fate of Protein Digestion Products in the Body*. III. The Absorption of Amino-Acids from the Blood and Tissues. *Jour. Biol. Chem.*, 1914, **16**, 197.

Urea⁵⁸ behaves in the same manner. That the intravenously injected uric acid does not enter into some combinations in the blood which prevents its determination by the Folin and Denis method is indicated by the ability to recover all uric acid which is added to blood *in vitro*.

From our studies and those of others it appears that more than 3 mg. per 100 c.c. of blood is a symptom of gout. But whether or not retention of uric acid after its intravenous injection, or after feeding substances containing purin or nucleins, is to be regarded as evidence of gout is open to question, since we have shown that the failure to eliminate exogenous uric acid is not peculiar to gout.

We are impressed with the importance of carrying out studies on uric acid elimination on persons who are really normal. It may be doubted whether some of the so-called normal subjects used for physiologic studies on uric acid elimination were not pathologic. Before considering an experimental subject as normal it is necessary that a thorough medical examination be made and that the modern laboratory tests, especially those for renal function, be employed.

CONCLUSIONS

1. More than 3 mg. of uric acid per 100 c.c. of blood, with the patient on a purin-free diet, is a symptom of gout, but it is not diagnostic of this disease.

2. No relation exists between the amount of uric acid and of total nonprotein nitrogen found in the blood of gouty persons.

3. A marked retention of nonprotein nitrogen is not frequent in gout.

4. The excretion of exogenous uric acid by normal, by arthritic, and by gouty persons varies greatly both in amount and in duration.

5. The retention of exogenous uric acid is a symptom of questionable importance in the diagnosis of gout.

We wish to thank Dr. Christian for allowing us to study the gouty patients in his wards. We are much indebted to Dr. Otto Folin for advice in the interpretation of certain findings. The three cases of insanity were studied at the Boston Psychopathic Hospital through the courtesy of Dr. E. E. Southard. One of the cases of gout was studied at the Massachusetts General Hospital through the cooperation of the orthopedic department.

58. Marshall and Davis: Urea: Its Distribution and Elimination from the Body. *Jour. Biol. Chem.*, 1914, **18**, 53.

THE FERMENT-ANTIFERMENT BALANCE AND ITS
RELATION TO THERAPEUSIS *

WILLIAM F. PETERSEN, M.D.

CHICAGO

For many years able and patient investigators have been occupied with the elaboration of the science of immunology. Numerous have been the achievements that have rewarded the direction of the foremost medical workers into these channels of thought and research; indeed, so splendid and satisfying have been many of them that we have gradually come to assume that therapeutic advance can take place only along these well demarcated lines. And yet, certain of the commoner infections have failed to yield to the intricate structure that has been reared in the effort to overcome them; failure which we have felt was due not to the method of attack, but to present limitations in the application of the theory by individual investigators. The study of tuberculosis illustrates the point most clearly. The end-result of innumerable immunologic studies has here left the problem of therapeusis practically unaltered; tuberculin therapy, introduced on a background of strictly immunologic research, while still offering the most favorable therapeutic result in selected cases, is no longer to be considered an immunizing agent in the specific sense of the term; the present time finds the laboratories devoted to tuberculosis research turning largely to studies along chemotherapeutic lines. It would seem justifiable, therefore, to explore the possibility of new avenues of approach to therapeutic problems; to determine whether or not some other broad basis can be found that, with proper study, will lead to fruitful therapeutic results. With this idea in mind the following outline is presented, not to be accepted as a completed study, but merely to offer briefly the rudiments of the problems when examined from a nonimmunologic standpoint.

The fundamental factor in overcoming bacterial intoxication not due to the soluble exotoxins lies in the ability of the cells or fluids of the invaded organism to digest the toxic protein fragments to their lowest degradation products and in this way overcome their deleterious effect. Digestion, too, no matter under what immunologic term we wish to classify the particular phase, must be considered the basis of the phenomena which have to do with overcoming bacterial invasion

* Submitted for publication July 25, 1917.

* From the Medical Clinic of Joseph L. Miller at the Cook County Hospital, and the Laboratory of Physiological Chemistry, College of Medicine, University of Illinois.

itself. Might it not be warranted; therefore, to study in greater detail these digestive forces and their relation to pathologic conditions, in the hope of eventually being able to control ferment activity and achieve therapeutic results thereby?

To Abderhalden and his school in Germany we owe the beginning of such a movement; unfortunately, the center of interest was nearly shifted from a study of fundamental phenomena to particularistic and technical details involved in the clinical popularization of the so-called Abderhalden test for pregnancy. Abderhalden was undoubtedly prejudiced in favor of the idea of the specificity of proteolytic ferments because of the beautiful specificity displayed by the ferments that hydrolyze the carbohydrates. When, however, one considers that the variety of carbohydrates with which ferments have to deal is relatively limited as contrasted with the practically endless combinations possible in the protein molecule, this prejudice is not necessarily logical. Possibly Abderhalden was influenced, too, by the immunologic conception of specificity; indeed, did hope to answer just this problem on the basis of highly specific proteases. The final demonstration that the Abderhalden reaction for pregnancy had not the merit of specificity emphasized by Abderhalden, unfortunately had a tendency to check further investigation in this field. Jobling was the first in this country to recognize the importance of, and to systematically study, ferment action in relation to pathologic conditions, and began his work some time previous to the investigations of Abderhalden in this particular line. In a series of some thirty odd articles,¹ a broad experimental foundation has been laid on which it seems possible to attempt clinical investigation along lines not previously considered. In order to correlate the ideas which underlie the following studies it may be advisable to discuss briefly in this article some of the phenomena which Jobling has studied.

Vaughn, Matthes and Krehl, Friedberger and numerous other investigators have established the relation between intoxication and fever and the causal relation of the protein split products thereto. We are therefore justified in assuming that with bacterial invasion the intoxication of the organism is due to bacterial proteins; there is also a possibility that the proteins of the host themselves may, under certain conditions, give rise to toxic split products; the source, however, need not for the moment concern us.

If we are justified in ascribing major importance to these protein derivatives, we are equally justified in studying the mechanism of detoxication, which must involve the proteolytic ferments that will break down the toxic complexes to nontoxic forms. Several proteolytic ferments may occur in the serum. (1) The leucoproteases: (a)

1. Jour. Exper. Med., 1912-1916, 16-23.

an alkaline active ferment capable of splitting native protein largely to the proteose stage; (b) an acid active ferment with a similar range of activity; (c) an ereptase, active in both acid and alkaline reaction and splitting partially hydrolyzed proteins to the amino-acid stage. These ferments are derived from disintegrating but not from living leukocytes, and the fluctuations in the leukocyte count have therefore no direct bearing on the amount of these ferments in the serum. Of the ferments of this possible derivation only the ereptase is able to act in the presence of blood serum and tissue fluids, because the true proteases are inhibited by the antiferment. In a localized area, however, the amount of such ferments liberated may be sufficient to saturate the antiferment, and in this case digestion can go the entire stage from native protein to amino-acid. (2) Serum protease: a polyvalent, trypsin-like ferment, active in neutral, or even in slightly acid or alkaline reactions, is completely inhibited by the antiferment. It becomes active in the body only when the antiferment is removed or diminished, and is able to digest any native protein to the amino-acid stage. It is present in small amounts in normal human serum, but in relatively large amounts in certain of the lower animals. (3) Serum peptidase: a polyvalent ferment active in the presence of the serum antiferment, able to digest partly hydrolyzed proteins to the amino-acid stage and active in reactions similar to those favorable for protease action. It is present in normal human serum in small amounts.

These ferments should not be confused with the alexin, or complement, which is slightly less resistant to heat and is destroyed by the lipid solvents. Whether or not these ferments always act in a lytic capacity, or may under certain conditions become synthetic, is a question as yet unsettled.

Inasmuch as the first two types of ferment are active only under special conditions and are not present in more than small amounts in the serum at any time, they are of relatively less import than the last ferment, the peptidase. It is at once apparent that we are dealing here with the detoxicating agent, a ferment that hydrolyzes proteins from the toxic stages — albumoses (proteoses) and peptones — to the non-toxic amino-acids. A mobilization of this ferment could then be considered only as of beneficial significance, never as a factor in the production of an intoxication, and, since it is active in the presence of the antiferment, the fluctuations of the latter in titer would have no effect on the detoxicating force. An increase in the amount of this ferment occurring spontaneously during the course of disease should, therefore, be coincident with clinical improvement and, conversely, the disappearance of the ferment should permit the accumulation of toxic split products and an increase in intoxication. An increase induced anti-

ficially, if possible, should be equally effective as a measure of detoxication.

When we turn to the true proteases we deal with a reaction of which the possibilities are more complex for two principal reasons: (a) the ferment action may involve the splitting of native proteins to the higher split products and may conceivably, at some time in the process, give rise to intoxication; (b) the ferment action is balanced by the presence of the antiferment, and we have therefore to deal with two variable factors. For simplicity we may take two concrete examples. Suppose that a pneumonic focus with its mass of cellular detritus and fibrin represents, for the normal tissue, simply so much foreign material from which it must free itself by digestion; as long as the autolysis of this foreign mass proceeds slowly, higher and toxic split products will be absorbed as such; digestion proceeds slowly, because the leukocytes are still living, and therefore not "shedding" their ferment as they should, and because of the great increase in the antiferment of the serum and tissue fluids which takes place early in the infection. According to the hypothesis presented, if the antiferment titer is now lowered and at the same time sufficient protease and peptidase are liberated, we might expect a temporary increase in the degree of intoxication (because of the rapid absorption of toxic split products) followed by a detoxication when autolysis is actively initiated. A therapeutic ideal might therefore be sought in just such an alteration of the ferment-antiferment balance.

Let us assume, on the other hand, that we are dealing with a quiescent tubercle with just sufficient encapsulation by scar tissue to prevent any excretion of toxic material from the focus. If, for any reason, the serum alteration above mentioned should occur in such a patient, we might expect a considerable degree of intoxication due to the digestion of the protective connective tissue and of the central necrotic mass, together with the liberation of accumulated toxic material preformed in the necrotic focus. Theoretically, it might seem warranted to endeavor to increase the antiferment in this condition in order to check protease activity and protect the tubercle from digestion. In a subsequent article this reaction and its relation to our present empirical therapy will be discussed in detail. It will be evident from the two examples outlined that fluctuations in the digestive balance of the tissues and serum may effect certain pathologic processes in a most fundamental way.

When considering the factors in the balance, it is apparent that we are compelled to consider the antiferment, or antitrypsin, as it is commonly designated, as an integral part of the mechanism under consideration. Here we enter the field of lipid bodies. The antiferment is not an antibody in the immunologic sense, although it was early so

considered; it consists of the highly dispersed unsaturated lipoids of the serum and lymph and its titer varies, therefore, with at least three conditions: (a) the amount of lipoids present; (b) the dispersion, and (c) the chemical structure; that is, the degree of unsaturation; all conditions that are subject to considerable variation and any one of which may account for wide fluctuations in the titer commonly observed. Thus, lessening the dispersion by acidifying, by salting and by heating to a sufficient degree, inactivates the antiferment; physical adsorption by certain chemically inert adsorbing surfaces lowers the titer; solution of the lipoids in chloroform and ether removes the antiferment from the serum. The most comparable substances, in their antitryptic property, which we have available, are the soaps of the unsaturated fatty acids. There is considerable ground for the belief that the antiferment lipoids are in more or less intimate physical combination with the serum albumin with which fraction they are thrown down on the usual methods of separation of the serum proteins.

It is known that the antiferment is greatly augmented during certain diseases, notably in the acute infections, in pregnancy, in carcinoma and cachectic states in general; following anaphylactic and other protein shock, and in certain pathologic processes in the central nervous system of a degenerative character; in other words, it forms part of a rather general "reaction" phenomenon. This seems purposeful, in that an increase in the antiferment power would tend to counteract the heightened destruction of the proteins of the body commonly observed in toxic conditions. The antiferment of the lymph stream is appreciably increased after feeding, although the increase in the blood stream is only moderate in amount; in starvation, on the other hand, the antiferment shows a progressive decrease.

We deal, then, with the probability that the antiferment may be augmented by selective diet, by shock therapy (including vaccines), and possibly by the intravenous injection of the proper lipoids. Another factor enters, however, into the regulatory mechanism, namely, the fact that the amount of lipoids in the serum is related to the lipolytic activity developed therein. That is, when the lipolytic activity is low, as for instance, in pregnancy, in carcinoma, in the acute infections and in advancing tuberculosis, an accumulation of lipoids will take place in the serum and, as a corollary, the antiferment titer will increase. Conversely, a strengthening of the lipolytic activity will metabolize the serum lipoids more rapidly and in this way decrease the antiferment titer. It is apparent, therefore, that the regulation of the antiferment titer is dependent on several factors, some of which may be amenable to artificial and therapeutic control.

Empirically, we have probably been doing precisely this in our use of iodine and the iodides. These are used therapeutically in a great

number of disease conditions, but chiefly, and with universal acceptance, to hasten the resolution of necrotic tissues, such as the gummas of late syphilis. It has been demonstrated experimentally that the iodids will increase the rate of autolysis to a considerable degree. Inasmuch as the effect is not found to be directly on the ferment, we must seek to find some other explanation. In this connection it was noticed in vitro experiments that the iodids lessened the antiferment titer of the serum, and later experiments carried out in clinical cases revealed that a lowering of the antiferment titer took place progressively under iodid therapy. We have then, it seems, one of the means of influencing the ferment-antiferment balance in common use.

The direct intravenous injection of ferments has not yet been used with success, because of the toxicity of the preparations employed. Hiss and Zinsser, in their interesting work commenced a number of years ago, employed leukocytic extract subcutaneously with encouraging results, although the possibility is not excluded, as Zinsser and Tsen point out in a recent article, that the results achieved are due to a general shock reaction rather than to the absorption of ferments. The direct increase of ferments is at least one method of approach worthy of further investigation.

If protein splitting with its resulting formation of toxic split products is at the basis of many of the intoxications with which we have commonly to deal in acute and chronic conditions, then the detoxication by means of ereptases and similar ferments should be of considerable importance. From experimental observations it seems probable, at any rate, that by means of alterations in the ferment-antiferment balance we may be able to attack certain therapeutic problems from this relatively simple point of view.

THE RELATION OF PELLAGRA TO LOCATION
OF DOMICILE IN INMAN MILLS,
INMAN, S. C.*

J. F. SILER, M.D.
Major, Medical Corps, U. S. Army

P. E. GARRISON, M.D.
Passed Assistant Surgeon, U. S. Navy

AND

W. J. MACNEAL, M.D.
NEW YORK

INTRODUCTION

In the immediately preceding paper¹ of this series, the section of this report dealing with geographical distribution of pellagra was begun by a detailed study of the relation of pellagra to domicile in Spartan Mills. That community was regarded as a fairly typical cotton mill village, but nevertheless it presented certain individual peculiarities. It was situated within the limits of a fairly large city. It was one of the oldest mills in the county. It possessed an organized social service for education of the people and a good hospital for the care of the employees. Very marked general sanitary improvements were made during 1913 and 1914, during the progress of our study there. The early history of pellagra in the village was obscure and the records of the population previous to the fall of 1913 were incomplete. Inman Mill Village may be contrasted with Spartan Mills in respect to these features. This mill village is located about twelve miles from Spartanburg City, near a small country station. It is one of the newer mills of the county, having been constructed in 1902. There was no provision for social service. The general sanitary arrangements of the community have remained much the same since the erection of the mill. The available records in regard to population within the mill village are exceptionally complete, in part, because a

* Submitted for publication May 3, 1917.

* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* This is the eleventh paper in the series now appearing in THE ARCHIVES, constituting the third report of the Robert M. Thompson Pellagra Commission. This paper has been written since Dr. Garrison and Dr. Siler were recalled to active service in the Medical Corps, U. S. Navy, and the Medical Corps, U. S. Army, respectively. They are, therefore, not responsible for the compilation of the data, nor for the deductions drawn from them.

1. The Relation of Pellagra to Location of Domicile in Spartan Mills, S. C., and the Adjacent District, THE ARCHIVES INT. MED., 1917, 20, 198.

permanent record of the tenants in the various houses has been kept in the office of the mill company, and, in part, because a house-to-house census of this village was made by us in 1912, a year earlier than in Spartan Mills. Because of these general differences from Spartan Mills, it seems important to present the detailed data in regard to the domiciliary relationship of pellagra in Inman Mill Village.

GENERAL DESCRIPTION OF THE VILLAGE

The community of Inman Mills² is situated in Campo Bello and Beech Springs Townships of Spartanburg County, about half a mile from Inman Station on the Asheville-Columbia division of the Southern Railroad and about twelve miles from Spartanburg City. There is a

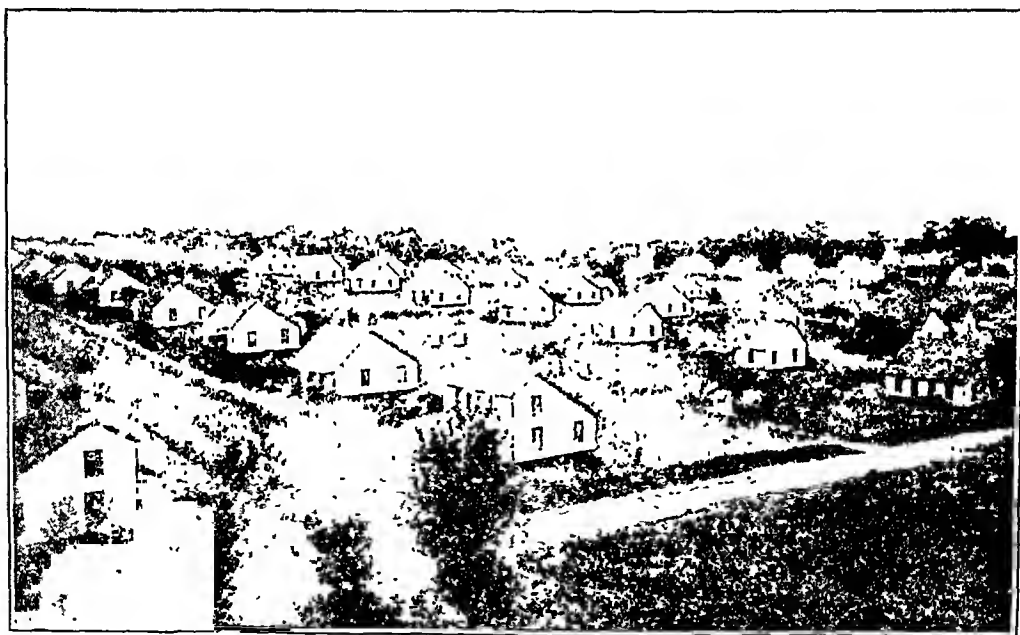


Fig. 1.—General view of Inman Mill Village looking southeast. The house in the middle foreground of the picture is 2 C Street.

small country village surrounding the railroad station, which provides a commercial and shipping center for the surrounding farming district. The mill village is a separate community and is surrounded by farms.

Previous to 1902 the site of the present mill was farm land. The mill was erected in 1902 and put into operation in September of that year. The motive power is steam and the manufactured products are the heavier grades of cotton cloth.

At the time when the mill was first opened in September, 1902, most of the houses situated on A, B, C, D and the north side of E

2. We are indebted to Mr. James A. Chapman, President of Inman Mills, for important information used in this section.



Fig. 2.—A typical house at Inman Mills. This is a front view of 17 D Street.



Fig. 3.—The two types of wells supplying water for domestic purposes at Inman Mills.

Streets were built and ready for occupancy. Three dwellings for negroes were also erected across the railroad track. In the following years houses were added on C, D and E Streets; in 1907, F Street was opened with 23 new houses and in 1913, G Street was opened with 10 houses on the north side, bringing the total number of dwellings to 120 in 1914. The mill houses are all of frame construction, built without cellars, most of them containing four or six rooms and arranged to accomodate two families. Besides the mill houses and the mill, the



Fig. 4.—Front view of a typical outhouse at Inman Mills. The type of garbage receptacle is also shown.

village contains a chapel situated on A Street, a store, a ten-room boarding house, designated as a hotel, and the superintendent's house on B Street.

Water for technical use and for fire protection is stored in a stand-pipe at the upper (east) end of C Street (See map, Fig. 5). The water for domestic use is obtained from wells, part of them driven wells with pumps and part of them open wells with chain and bucket.

The location of these wells is indicated on the map. The method of disposal of human excreta is by means of open surface privies, provided, in part, with metal pails. Ultimate disposal is by scavenger service. The location of the privies is indicated in Figure 1 and also on the map (Fig. 5).

A general view of the village is shown in Figure 1. A typical house is shown in Figure 2. Figures 3 and 4 show the types of wells and the type of privy, respectively.

Insects.—The house fly (*Musca domestica*) is very abundant during the warmer season. The stable fly (*Stomoxys calcitrans*) is present in considerable numbers. During 1912, 1913 and 1914 the cows were kept in a pasture separate from the dwelling houses, but nevertheless the stable flies were usually present about the houses and often constituted a pest to persons on the porches. The bedbug (*Cimex lectularius*) is present in practically every house, and construction of the houses makes its eradication very difficult. The head louse (*Pediculus capitis*) is common on the children. Practically every child had been infested with this parasite at some time. Especially the children in school and those at work in the spinning room of the mill are commonly infested. The body louse (*Pediculus vestimenti*) has not been observed and the people appear not to be acquainted with it. The sand fly (*Simulium*) has not been observed in this village, although there are potential breeding places in the vicinity.

Population.—At Inman Mills the population was drawn chiefly from the neighboring mill villages and from the outlying farms. The inhabitants were of the usual mill type found in these villages. A noticeable feature of these people was their migratory tendency. Because of inefficiency, through ignorance or general inferiority, they easily became discontented and roamed from mill to mill, staying at a town only a few months, or even weeks. A large proportion of the residents at Inman in each year consisted of these transients. Moreover, of the more permanent residents of the village many moved about from house to house within the town. It was, therefore, not surprising to find that a single house list often contained the record of as many as five or six families during one year. In fact, of the 118 families canvassed in 1912, the first year of our census, only 26 still occupied the same house in October, 1914.

The tendency to change residence was observed in pellagrous as well as in nonpellagrous households. Of the twenty-four pellagrins incident at Inman in 1912 and 1913, only nine remained continuously in the same house from onset to the end of our survey. This migratory

tendency of the population, as a whole, will explain in great part the comparatively large size of the second zone in each year.

In Table 1 the total white population, as recorded in our three house-to-house canvasses, is shown distributed according to sex and age in each year, 1912 to 1914, inclusive. It may be noted that the yearly totals in Table 1 represent only those persons actually present in the village during the respective census. These population totals do

TABLE 1.—DISTRIBUTION OF THE WHITE POPULATION OF INMAN MILLS, ACCORDING TO SEX AND AGE, IN EACH YEAR

Age	1912			1913			1914		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0-4	44	55	99	54	77	131	57	65	122
5-9	45	39	84	44	54	98	49	57	106
10-14	30	23	53	35	23	58	42	33	75
15-19	27	31	58	45	34	79	46	29	75
20-24	22	16	38	47	43	90	35	29	64
25-29	16	12	28	25	23	48	29	14	43
30-34	12	25	37	24	33	57	19	31	50
35-39	12	7	19	14	18	32	24	23	47
40-44	4	4	8	10	13	23	10	14	24
45-49	5	4	9	7	5	12	6	11	17
50-54	2	2	4	4	7	11	7	5	12
55-59	6	1	7	7	2	9	6	5	11
60-64	3	3	6	5	6	11	4	7	11
65-69	0	1	1	3	2	5	4	0	4
70-74	1	0	1	1	1	2	0	1	1
75-79	0	0	0	0	0	0	0	0	0
Over 80	0	0	0	0	0	0	0	0	0
Age unknown	81	93	180*	5	12	17	2	2	4
Total	310	316	626*	330	353	683	340	326	666

* Including six individuals whose age and sex were not ascertained.

not correspond, therefore, to those shown in Tables 12, 13 and 14 (summarized in Table 11), which include the entire number of individuals recorded in the mill house lists during the respective year. The average size of families among these mill workers was five persons.

The colored population in this town was very small, as shown in Table 2. With few exceptions, negroes were not employed as house servants in this village, although some of the colored women did cook-

ing and laundry work for the residents. The adult negro males were laborers or engaged in heavy work about the mill.

Industrial and Economic Conditions.—The wages paid at this mill have been somewhat lower than at Spartan Mills. In July, 1914, the mill employed 183 men over 16 years of age, fifty-three boys under 16 years, seventy-seven women over 16 years of age and twenty-eight girls under 16 years. The average daily wage in this month was \$1.15

TABLE 2.—DISTRIBUTION OF THE NEGRO POPULATION OF INMAN MILLS, ACCORDING TO SEX AND AGE, IN 1913 AND 1914

Age	1913			1914		
	Female	Male	Total	Female	Male	Total
0-4	0	1	1	2	0	2
5-9	0	1	1	2	1	3
10-14	3	0	3	3	1	4
15-19	0	4	4	1	4	5
20-24	0	0	0	1	0	1
25-29	0	0	0	2	0	2
30-34	0	0	0	1	0	1
35-39	1	1	2	0	0	0
40-44	1	0	1	1	1	2
45-49	0	0	0	1	0	1
50-54	0	1	1	0	2	2
55-59	0	0	0	0	0	0
60-64	0	0	0	0	0	0
65-69	0	0	0	1	0	1
70-74	0	0	0	0	0	0
75-79	0	0	0	0	0	0
Over 80	0	0	0	0	0	0
Age unknown	0	0	0	0	0	0
Total	5	8	13	15	9	24

for the men, 58 cents for the boys, 87 cents for the women and 63 cents for the girls. The relation between the mill company and its employees is closer here than at Spartan Mills, because the mill and its village form a definite unit rather isolated from other communities. A large share of the supplies for the people are handled by the company store because it is the only one close at hand.

General Dietary.—The dietary was investigated by personal interview at the home of every family in 1912, and 1913, and dietary

changes were inquired into in 1914. In general, it may be said that the diet differs from that of the people in Spartan Mills by approaching the diet of the rural population. Much less fresh meat was eaten at Inman Mills during the years of our inquiry. On the other hand, more than half the families kept a cow and chickens and the use of milk and eggs was much greater here. Practically every family had a large garden, the allowance of ground space being more ample than at Spartan Mills. Compound lard, containing cottonseed oil, was used

TABLE 3.—DISTRIBUTION OF THE WHITE MILL OPERATIVES RESIDING IN INMAN MILLS, ACCORDING TO SEX AND AGE, IN 1913 AND 1914

Age	1913			1914		
	Female	Male	Total	Female	Male	Total
Under 12	1	1	2	1	0	1
12-14	17	10	27	12	17	29
15-19	32	39	71	37	24	61
20-24	21	46	67	21	27	48
25-29	5	21	26	9	11	20
30-34	8	31	39	5	29	34
35-39	1	21	22	4	23	27
40-44	0	8	8	1	13	14
45-49	0	3	3	0	7	7
50-54	1	5	6	0	1	1
55-59	0	0	0	0	4	4
60-64	0	3	3	0	3	3
65-69		3	3		0	0
70-74	0	1	1	0	1	1
75-79	0	0	0	0	0	0
Over 80	0	0	0	0	0	0
Age unknown	5	4	9	1	4	5
Total	91	196	287	91	164	255

by every family in Inman Mills in 1913. In other respects the dietary was not different from that of the population at Spartan Mills. The frequency of use of certain articles of diet in this village has been discussed in detail in our Second Progress Report, where Inman Mills was designated as Mill Village 1.

Prevailing Diseases.—The acute infections of childhood prevailed in epidemic form every few years. Diarrhea and dysentery were prevalent throughout the warm season, among both children and

adults. Local epidemics of typhoid fever were frequent, usually attacking several families in neighboring houses, while the rest of the village escaped. Pulmonary tuberculosis and hookworm disease were not observed. Indigenous malaria did not occur.

HISTORY OF PELLAGRA AT INMAN MILLS IN THE YEARS
PREVIOUS TO 1912

The first known case of pellagra at Inman Mills was Pellagrin 37, a woman aged 32 years, who developed an initial erythema at 3 E Street in 1908. The exact time of onset in this case is not quite certain, for although the patient says that her erythema appeared while living in this house in the fall of 1908, the mill records show that the family resided at 3 E Street only until Aug. 31, 1908. It is, therefore, most probable that Pellagrin 37 actually developed the disease sometime earlier in the summer of that year. The only recorded symptom in this first attack was the characteristic erythema, which appeared on the hands "after washing with Gold Dust," and did not subside until well into the winter. Pellagrin 37 had lived at Inman Mills since 1903 and in this particular house since Feb. 13, 1907, although her husband told us that prior to onset of pellagra, she had made frequent long visits at her mother's house in another mill village conspicuous for its many cases of pellagra. On Aug. 31, 1908, Pellagrin 37 moved to 13 E Street, where she resided until Nov. 15, 1908, when she removed to 24 F Street. She is indicated on the map (Fig. 5) at 3 E Street, the house of origin, by a solid circle and at the two subsequent residences by hollow circles. There were no other known cases of pellagra at Inman in 1908.

In 1909 Pellagrin 37 suffered a recurrence in the spring, while living at 5 D Street, where she had moved on Jan. 16, 1909. She went to the State Hospital for the Insane at Columbia, July 15, 1909, and except for brief visits at home, she remained there until April, 1911. Her residence at 5 D Street has been indicated by a hollow circle on the map (Fig. 5), and her residence at 24 F Street, although of only fifteen days' duration in 1909, has been designated likewise. A second case of pellagra appeared in this village during this year. At 1 C Street Pellagrin 318, a man aged 52 years, developed his initial erythema in July, 1909. He was a millworker who had lived in Inman Mills since 1904 and in the house at 1 C Street for more than two years. Early in the spring, 1909, he began to be troubled with diarrhea, which was later followed by erythema of the hands, with several repetitions of redness and peeling, accompanied by a persistent sore mouth. He was taken to Columbia for treatment, remaining there until January, 1910. On the map (Fig. 5), Pellagrin 318 has been indicated by

a solid circle at the house of origin, 1 C Street. These two cases, Pellagrins 37 and 318, are the only pellagrins definitely known to have resided at Inman Mills in 1909.³

In 1910 Pellagrin 318 died of pellagra at his home at 1 C Street, shortly after his return from the hospital at Columbia. Pellagrin 37, who had been at the Columbia State Hospital since the previous summer, suffered a recurrence in the spring, 1910. She returned to her family, who were living at 5 F Street, in the latter part of April, but within a week's time was obliged to go back to Columbia. In July, 1910, she returned to Inman Mills and stayed at 5 F Street with her family until Oct. 15, 1910, when they all moved to 2 E Street. Again in December, 1910, Pellagrin 37 went to Columbia for treatment, remaining there until April, 1911. Pellagrins 318 and 37 have been designated at their respective residences in 1910 by hollow circles on the map (Fig. 5). There was one case of pellagra apparently incident at Inman Mills in 1910, namely, Pellagrin 366, a woman aged 24, who developed an initial erythema at 21 F Street. She had lived in this house since Feb. 1, 1910, coming here from another mill village in which pellagra was very prevalent. Details in regard to this first attack are lacking, but it is possible that the origin of this case was outside of Inman Mills. Pellagrin 366 has been designated, however, by a solid circle at 21 F Street, the apparent house of origin. Another patient who may possibly have contracted pellagra at Inman Mills in 1910 was Pellagrin 883, a woman aged 31 years, who developed her initial erythema in April, 1911. She lived at 6 C Street from March 1, 1910, until Jan. 5, 1911. From this house, which may be the house of origin, she went to live on a farm outside of Inman Mills and her initial attack occurred at this latter residence. She has been indicated at 6 C Street by a circle containing a cross. At 3 F Street Pellagrin 198, a man aged 40 years, resided from June 4, 1910, to Nov. 30, 1910, in next-door relationship to Pellagrin 37, who lived at 5 F Street and later at 2 E Street. From Inman Pellagrin 198 moved to 397 Arch Street, Spartan Mills, where he remained until January, 1911. In January, 1911, he moved to 343 College Street in the same village. His initial erythema appeared during a short stay at Liberty Mill in March,

3. At 10 D Street Pellagrin 333, an elderly woman, lived with her daughter during the fall and winter, 1909 and 1910. From March 16, 1910, to May 15, 1911, the family lived at 3 D Street. Late in the winter, 1911, they moved to 12 C Street and remained there until Jan. 12, 1912, when the mother left Inman Mills and went to live with one of her sons, at whose house she died of pellagra, June 15, 1912. According to her daughter's statement, Pellagrin 333 had suffered from the disease since 1908 and it is probable that she was an old case. Our information, however, seems too meager to permit of a diagnosis earlier than 1912, in which year she is known to have died of pellagra, and she has, therefore, not been included as a pellagrin at Inman Mills.

1911, within four months of the termination of his exposure at Inman Mills. He has been considered possibly incident at each of the three residences cited above, but in all probability the actual house of origin was 3 F Street, where he has been indicated by a circle containing a cross. There were no other definite cases of pellagra known to be at Inman in 1910.⁴

In 1911 several pellagrins who had contracted the disease elsewhere moved to Inman Mills. Pellagrin 514, who had had her initial attack in that summer, came to live at 1 A Street, Dec. 10, 1911. A 9 F Street Pellagrins 91 and 93, both of whom had shown active symptoms earlier in the year, resided from Nov. 22, 1911, to the end of that year. Pellagrin 163 lived at 13 F Street from Sept. 21, 1911, until the following spring. She had a recurrence in 1911 and again in 1912. Pellagrin 726, incident earlier in the summer at Spartan Mills, lived at 18 F Street from June 29, 1911, until Sept. 30, 1911. Pellagrin 145, who had her initial attack in 1904 and had suffered recurrences each spring thereafter, moved to 17 D Street Dec. 4, 1911. Pellagrin 328, who had developed some premonitory symptoms of pellagra at Spartan Mills, came to 9 E Street Nov. 16, 1911, and suffered her initial erythema here early in 1912. These seven cases have been indicated at their respective residences by hollow circles on the map (Fig. 6). In addition to these moved-in cases there were two old resident pellagrins at Inman Mills in 1911, namely, Pellagrin 37, who returned from Columbia in April, 1911, to her home at 2 E Street, and Pellagrin 366, who lived at 21 F Street until Aug. 31, 1911, and subsequently at 22 F Street until the middle of November, 1911, when she moved from the village. Both of these patients suffered recurrences in 1911 and have been indicated at their respective residences by hollow circles on the map (Fig. 6).

There were four pellagrins incident at Inman Mills in 1911. Pellagrin 319, aged 32 years, was the daughter of Pellagrin 318, who had died at 1 C Street in January, 1910. During the year following her father's death, Pellagrin 319 had not been strong, but she had not shown any definite pellagrous erythema until the spring of 1911. She died at her home at 1 C Street Aug. 13, 1911. A second case incident at this mill was Pellagrin 160, a girl 17 years old, who showed an initial erythema in June, 1911, at 16 C Street, where she had lived since Oct. 1, 1910. The third case was Pellagrin 592, a woman aged 19 years,

4. Pellagrin 329, mother of Pellagrins 198, 326 and 328, frequently visited a son at Inman Mills during his residence at 10 F Street from May, 1910, to February, 1911. It is possible that she was a pellagrin at this time, although, for lack of definite information, she has been classed as incident later in 1911 at Spartan Mills. She is known to have had a definite attack of pellagra which ended fatally in October, 1911.

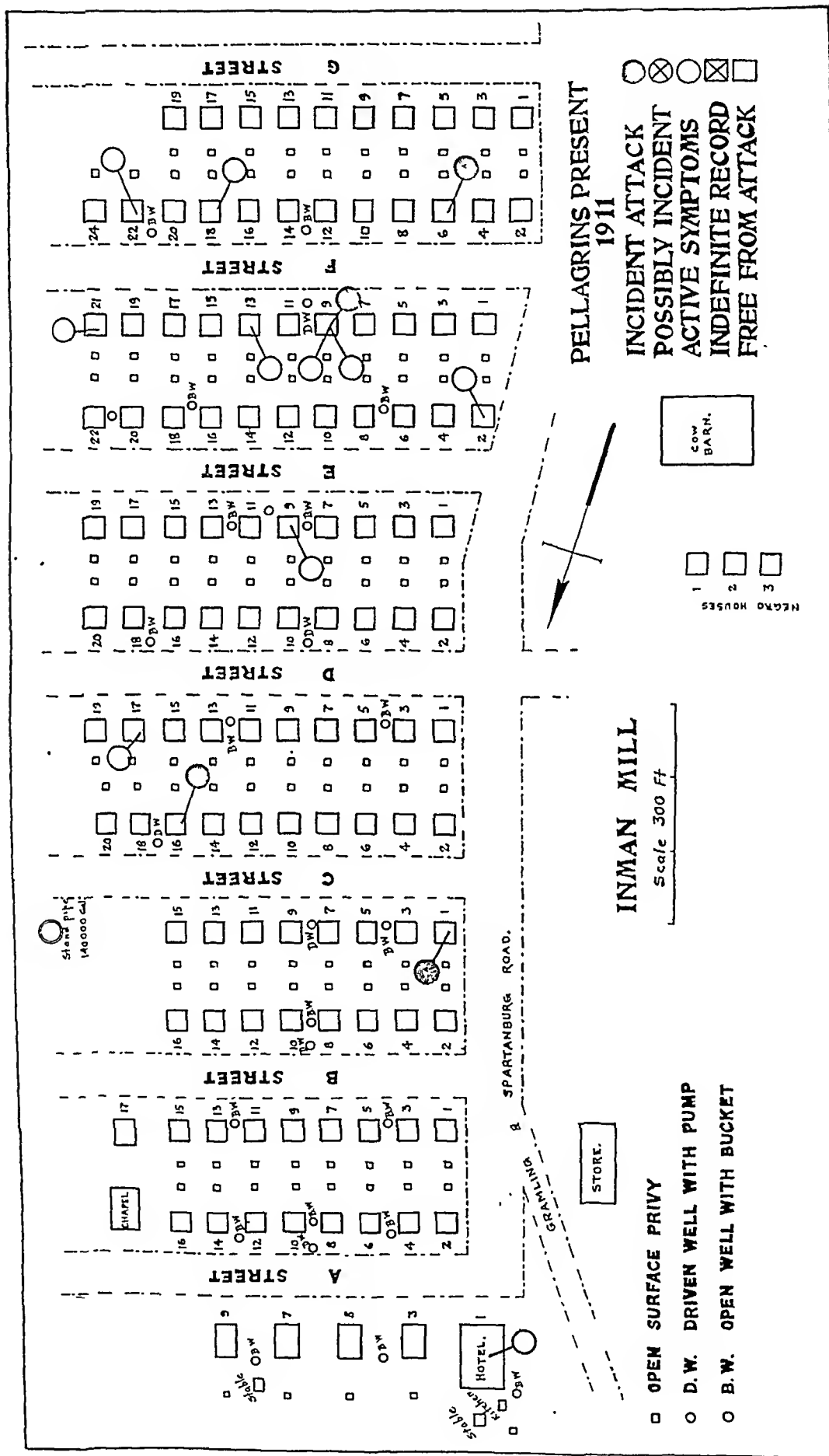


Fig. 6.—Map of Inman Mills, showing pellagrins present in 1911.

who developed initial symptoms of the disease in June, 1911, at 9 F Street, where she had been living since Jan. 18, 1911. Previous to this residence she had lived in a town where pellagra was prevalent. She moved away from Inman Mills Aug. 31, 1911, but returned in 1913. A fourth case, probably incident in this year, was Pellagrin 316, a man

TABLE 4.—PELLAGRINS RESIDING IN INMAN MILLS IN EACH YEAR FROM 1908 TO 1911, INCLUSIVE

Pellagrins	1908	1909	1910	1911	Sum
Definitely incident.....	1	1	1	4	7
Possibly incident.....	0	0	2	0	2
Recurrent.....	0	1	2	8	11
Without symptoms.....	0	0	0	0	0
With indefinite record.....	0	0	0	0	0
Total.....	1	2	5	12*	20

* Pellagrin 328 has not been included in this table. She appears to have contracted pellagra at Spartan Mills in 1911, and she moved to Inman Mills in November, 1911, where her initial erythema appeared early in 1912

TABLE 5.—PELLAGRINS INCIDENT IN INMAN MILLS IN EACH YEAR FROM 1908 TO 1911, INCLUSIVE

House	Residence Period	Onset	Pellagrin	Sex	Age
3E	Feb. 13, 1907 - Aug. 31, 1908.....	Summer, 1908	37	F	32
1C	Jan. 26, 1907 - Jan., 1910.....	July, 1909	318	M	52
6C	Mar. 1, 1910 - Jan. 5, 1911.....	April, 1911	883*	F	31
3F	June 4, - Nov. 30, 1910.....	March, 1911	198*	M	41
21F	Feb. 1, 1910 - Aug. 31, 1911.....	1910	366	F	24
1O	Jan. 26, 1907 - Aug. 13, 1911.....	Spring, 1911	319	F	32
16C	Oct. 1, 1910 - Mar. 31, 1912.....	June, 1911	160	F	17
6F	Feb. 16, 1910 - Aug., 1911.....	1911	316	M	65
9F	Jan. 18, 1911 - Aug. 31, 1911.....	June, 1911	592	F	19

* Origin probably here; first erythema appeared after moving away.

aged 65 years, who had lived at 6 F Street since Feb. 16, 1910. He died of pellagra in August, 1911. It is possible that he had the disease in 1910, but he has been classed in 1911 for lack of more definite history. These four incident cases have been indicated at their respective residences by solid circles on the map for 1911 (Fig. 6).

Table 4 presents a summary of the pellagrins definitely known to have resided at Inman Mills in the years preceding 1912. The data

for these earlier years are incomplete, as our field work at this mill did not commence until 1912. The pellagrins whose incidence may be traced with some degree of certainty to residence in this mill village are summarized by apparent house of origin in Table 5 for all years to 1911, inclusive. No attempt has been made to correlate incidence of pellagra with location of domicile in these earlier years, although when antecedent pellagra has existed in the immediate vicinity, it has been noted so far as the records permit.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1912

Our field work at Inman Mills began in July, 1912, and this particular community was more intensively studied than any other in that year. The first house-to-house canvass and census of the population was made at Inman Mills in 1912, an intensive method of study which was first applied to other communities in 1913. The data for the year 1912 are, therefore, more accurate and more complete here than for other villages, but, of course, considerably less complete even for Inman Mills than for the year 1913, because the work began rather late in the pellagra season of 1912 without any previous study of this population.

The data for the year 1912 are presented in detail in Table 12. Each house has been set down in turn and its occupants have been assigned to Zone 1, Zone 2 or Zone 3, in accordance with the rules adopted for the domicile study. The zone relationship has been determined entirely by the relation of domicile to an active case of pellagra: that is, to a pellagrin who manifested activity of the disease in the respective year or in the immediately preceding year. Pellagrins who had been free from attack of the disease for two years were excluded from consideration as centers for this zone study. Those nonpellagrous persons who resided in the same house with an active pellagrin for a period of at least two weeks in 1912 were assigned to Zone 1 in this year. If any one of these persons developed an attack of the disease later than two weeks after the beginning of domiciliary exposure and within a reasonable period after the termination of such exposure, the incidence of the disease was credited to Zone 1. This reasonable period has been arbitrarily limited to three months during the warmer season, from April 1 to October 1, and to six months, when all or part of the period fell in the colder season, from October 1 to April 1. Those nonpellagrous persons who resided in a house next door to an active pellagrin for a period of at least two weeks were assigned to Zone 2, unless, because of preceding and subsequent residence in Zone 1 within the reasonable incubation period, they were still considered as subjects of that zone. Any cases developing among these persons later than two weeks after the beginning of the exposure and within a reasonable

period after its determination have been credited to Zone 2. Those nonpellagrous persons who resided in this community in a house farther away than next door from an active pellagrin, have been assigned to Zone 3, unless, because of definitely known preceding and subsequent residence in Zone 1 or Zone 2 within the reasonable incubation period, they were still considered as subjects of either of these zones. Any cases of pellagra developing among these persons have been assigned to Zone 3. This plan is the same as that followed in the domiciliary study of Spartan Mills,¹ presented in the immediately preceding paper of this series, where fuller discussion of this plan may be found. It will be noted that pellagrins for whom the records are incomplete would tend to fall into Zone 3, because cases without known domiciliary association have been placed here.

During 1912 there were ten pellagrins residing at Inman Mills who had suffered from the disease in a previous year or who were incident elsewhere. Eight of these were living at Inman Mills early in the year and the two others moved in after the pellagra season. These cases are indicated by hollow circles on the map for 1912, Figure 7. One of them, Pellagrin 328, came to 9 E Street from Spartan Mills Nov. 16, 1911. At the previous residence she had nursed her mother, Pellagrin 329, until her death from pellagra in October, 1911. The daughter suffered from sore mouth and diarrhea at Spartan Mills, but the diagnosis of pellagra was not considered to be definite until early in the spring of 1912, when she developed an erythema on the backs of her hands while residing at 9 E Street, Inman Mills. It is possible, however, that she did have an erythema at Spartan Mills in 1911. The interval between the termination of the first-zone exposure at Spartan Mills and the appearance of the erythema at Inman Mills was less than six months in any case, and she has, therefore, been considered incident at the earlier residence and has been designated as a pellagrin moving into Inman Mills with the disease. She moved from 9 E Street to 12 D Street April 30, 1912, and is designated by a hollow circle at both these houses. Pellagrin 636 came to 24 F Street Oct. 24, 1912, having suffered a recurrent attack of pellagra earlier in the year at a farm in another part of the county. Seven of the other pellagrins suffered recurrences of pellagra at Inman Mills in 1912. Some of them moved during the year, so as to appear at more than one place on the map. Pellagrin 160 moved from 16 C Street to 3 C Street. Pellagrin 163 is shown at 13 F Street and again at 5 B Street, where she visited. Pellagrin 883, who had her first erythema in 1911, remained free from symptoms of pellagra during 1912 and is indicated by a hollow square at 7 F Street. Three pellagrins incident at Inman Mills in 1912 subsequently moved into other houses and are there designated by hollow

circles, namely, Pellagrins 150 and 315 at 5 A Street and Pellagrin 280 at 11 F Street.

According to the detailed data of Table 12, there were sixteen pellagrins incident at Inman Mills in 1912. Brief data in regard to these cases are summarized in Table 6, and they are indicated on the map for 1912, Figure 7, by solid red circles.

Six of these have been assigned to Zone 1. Pellagrin 113, an unmarried woman aged 20 years, came to the boarding-house at 1 A Street April 10, 1912. She had been at Inman Mills for eight months and had been living at 15 D Street previous to April 10, next door to

TABLE 6.—PELLAGRINS INCIDENT AT DEFINITE HOUSES AT INMAN MILLS IN 1912

House	Residence in House	Zone	Residence in Zone	Onset Date	Pellagrin	Sex	Age
1A	Apr. 10, 1912 - Aug., 1912.....	1	Apr. 10, 1912 - June 25, 1912	July 14, 1912	113	F	20
16A	Since Nov. 1, 1908.....	3	1907 - June, 1912.....	June, 1912	152	M	47
16A	Since Nov. 1, 1908.....	3	1907 - June, 1912.....	June, 1912	157	M	6
4B	Since Mar. 10, 1910.....	2	Apr. 1, 1912 - June, 1912....	June, 1912	164	F	30
5B	Since Apr. 24, 1911.....	2	Jan. 1, 1912 - July 1, 1912...	July 1, 1912	114	F	18
3C	Since Apr. 1, 1912.....	1	Since June, 1911.....	June, 1912	161	F	56
15D	Since Jan. 1, 1911.....	2	June, 1911 - July 15, 1912....	July 15, 1912	148	M	6
15D	Since Jan. 1, 1911.....	2	June, 1911 - July 15, 1912....	July 15, 1912	149	M	4
17D	Since Dec. 4, 1911.....	1	Since spring, 1904.....	Aug. 1, 1912	146	M	6
17D	Since Dec. 4, 1911.....	1	Since spring, 1904.....	Aug. 1, 1912	147	M	3
18D	May 14, 1912 - June 13, 1912....	2	July 1, 1911 - June 13, 1912..	July, 1912	280	F	19
7E	Since Nov. 23, 1911.....	1	Since Apr., 1912.....	June, 1912	153	F	7
7E	Since Nov. 23, 1911.....	2	Spring, 1912 - Apr., 1912....	Apr., 1912	154	F	5
13F	Sept., 1911 - Mar. 18, 1912.....	1	June, 1909 - Mar. 18, 1912....	Summer, 1912	884	F	20
13F	June 18, 1912 - Aug. 20, 1912....	2	July, 1912 - Aug. 20, 1912....	Aug. 21, 1912	315	F	20
15F	Mar. 13, 1912 - July 18, 1912....	3	Mar. 18, 1912 - Aug. 1, 1912..	Aug. 1, 1912	150	F	16

a pellagrin at 17 D Street and one at 16 C Street. At 1 A Street she was in the same house with Pellagrin 514, who suffered her first attack in 1911 and a recurrent attack in May, 1912, shortly after the arrival of this young woman. Pellagrin 514, who was the woman in charge of the boarding-house, left June 25, 1912. Pellagrin 113 had a sore mouth during the latter part of June and she developed her initial erythema July 14, 1912. She was brought to the Post-Graduate Hospital in New York for treatment and has remained free from recurrence since 1912. The second case in Zone 1, Pellagrin 161, was a woman 56 years old, whose daughter, Pellagrin 160, had suffered an initial attack in June, 1911, at 16 C Street. The family lived at 16 C

Street until April, 1912, and then moved to 3 C Street. The daughter, Pellagrin 160, suffered a recurrent attack in June, 1912, and the mother, Pellagrin 161, had her initial attack in the same month. The third and fourth cases in Zone 1, Pellagrins 146 and 147, were brothers, aged 6 years and 3 years, respectively. They had lived at 17 D Street since Dec. 4, 1911. Their mother, Pellagrin 145, had her initial attack in 1904 and had suffered recurrences every year since. Both children developed pellagra about Aug. 1, 1912. The older boy had the erythema on his hands and feet, while the younger, Pellagrin 147, showed the erythema only on the feet. In 1913 these children remained free from manifestations of pellagra, but in 1914 they both had mild recurrences of the disease. The fifth case in Zone 1 was Pellagrin 153, a girl 7 years old, living at 7 E Street. Her sister, Pellagrin 154, suffered her initial attack of pellagra about April 1, 1912, and this little girl, Pellagrin 153, developed the disease in June, 1912, more than two months later, while living in the same house. The sixth case in Zone 1, Pellagrin 884, a woman aged 20 years, lived with her mother, Pellagrin 163, at 13 F Street from Sept. 21, 1911, to March 18, 1912. She then went to a farm a few miles away, where she developed her initial erythema in the summer. The exact date of the appearance of the erythema was not ascertained, and there is no record of possible association with pellagrins at the new residence at the farm. The case has, therefore, been designated as incident in Zone 1 at 13 F Street.

The total number of exposed persons in Zone 1 in 1912, according to Table 12, was 129. The appearance of six new cases of pellagra in this zone indicates, therefore, an incidence rate of 4.65 per cent.

Seven of the incident pellagrins in Table 6 have been assigned to Zone 2. Pellagrin 164, a woman 30 years old, suffered her initial attack at 4 B Street in June, 1912. She had resided in this house since March 10, 1910. In 1911 her house was in next-door relationship to Pellagrin 319 at 1 C Street, who had an initial attack early in 1911, ending in death in August, 1911. Again, after April, 1912, her house came into the second zone, because Pellagrin 160 moved to 3 C Street in that month. About two months later, Pellagrin 164 suffered her initial attack in the house at 4 B Street, directly behind 3 C Street and adjacent to it. The second case in Zone 2, Pellagrin 114, a girl 18 years old, had lived at 5 B Street with her parents since April, 1911. From Jan. 1, 1912, until March 27, 1912, her home was in next-door relationship to Pellagrins 91 and 93, who lived at 8 A Street during that time. Her residence came again into the second zone in June, 1912, when Pellagrin 164 developed her initial erythema at 4 B Street. Pellagrin 114 had her initial erythema July 1, 1912, and has been designated as incident in the second zone in relation to Pellagrin 164, although,

according to the rules of this study, she would have fallen into the second zone in relation to Pellagrins 91 and 93 at 8 A Street, if her erythema had appeared one day earlier. Another possibly important source of exposure in this case requires mention, although it cannot enter into the statistical calculations. This girl, Pellagrin 114, was a very frequent visitor at the home of her aunt, Pellagrin 163, at 13 F Street from September, 1911, to March 18, 1912, and after March this aunt came to her house at 5 B Street and remained for several days, apparently less than two weeks. The available information in regard to this relationship, therefore, does not permit the classification of Pellagrin 114 in Zone 1. The third and fourth incident cases in Zone 2 were Pellagrins 148 and 149, brothers aged 6 years and 4 years, respectively, living at 15 D Street. These children had lived in this community since birth and at this house since Jan. 1, 1911. Their residence came into the second zone in relation to Pellagrin 160 at 16 C Street from June, 1911, to April, 1912. On Dec. 4, 1911, Pellagrin 145 moved into another adjacent house, 17 D Street, and she continued to live there, so that 15 D Street remained in the second zone in relation to her until its own cases of pellagra developed. In fact, the two little boys, Pellagrins 148 and 149, were intimate playmates of the children at 17 D Street and spent much of their time playing in and about that house. They both developed the initial erythema about July 15, 1912, and, as has been noted in the discussion of Zone 1, their two playmates, Pellagrins 146 and 147, sons of Pellagrin 145 at 17 D Street, developed the disease about Aug. 1, 1912. Here were four little boys, aged 3 to 6 years, living in adjacent houses, in one of which an old pellagrin, mother of two of the children, resided. All four of the children came down with pellagra within an interval of approximately two weeks. All four of these children had had measles at about the same time in May and June, 1912. The fifth case in Zone 2, Pellagrin 280, was a married woman 19 years old. She lived at 13 C Street from July 1, 1911, until April 24, 1912, in next-door relationship to Pellagrin 160 at 16 C Street until April. From May 14, 1912, to June 13, 1912, she lived at 18 D Street, just across the street from Pellagrin 145 at 17 D Street. She then moved to 11 F Street, where her initial erythema appeared in July, 1912, within three months after her exposure at 18 D Street, which has, therefore, been designated as the house of origin of her disease. On the map, Figure 7, she is indicated by a solid circle at 18 D Street and her subsequent residence at 11 F Street is indicated by a hollow circle. She becomes the fifth case originating in the same house with or next door to Pellagrin 145 at 17 D Street, all five of the new pellagrins having the initial attack in July or about Aug. 1, 1912, which is somewhat later than the usual time for the beginning of pel-

lagra in Spartanburg County.⁵ These facts suggest a common causative factor for all five of these cases and their residence in proximity to Pellagrin 145 shortly before the development of the disease would appear to challenge attention. The sixth case in Zone 2, Pellagrin 154 at 7 E Street, was a girl 5 years old, who had lived in this house since Nov. 23, 1911, next door to Pellagrin 328 at 9 E Street. The little girl showed her initial erythema early in April, 1912. Her older sister, Pellagrin 153, developed the disease later in 1912, and has been discussed in the group of first-zone cases. The seventh case in Zone 2 was Pellagrin 315, a married woman 20 years old, who lived at 13 F Street from June 18 to Aug. 20, 1912. This house had been vacated by Pellagrin 163 March 18, 1912, and was in next-door relationship to Pellagrin 280 from the onset of her pellagra in July. Aug. 20, 1912. Pellagrin 315 moved to 5 A Street where she developed her initial erythema within a week. She has been designated as incident in the second zone at 13 F Street, where she is indicated on the map, Figure 7, by a solid circle. Her subsequent residence at 5 A Street is indicated by a hollow circle. She left Inman Mills in September, 1912.

The total exposed population in Zone 2 in 1912, according to Table 12, was 587 persons. The seven incident pellagrins in this population give an incidence rate of 1.19 per cent. for this zone in 1912.

There were three cases of pellagra incident in 1912 at Inman Mills in the population living farther away than next door from an active pellagrin for a reasonable period before the disease appeared and, therefore, assigned to Zone 3. At 16 A Street a family in comfortable financial circumstances had resided since November, 1908. Their home at 16 A Street was in the more desirable section of the mill village, close to the superintendent's house, a section in which the older residents, the more efficient and better paid members of the community tended to accumulate, so far as such a tendency was manifest at all at Inman Mills. In this family the father, Pellagrin 152, aged 47 years, and the youngest son, Pellagrin 157, aged 6 years, both developed pellagra about the middle of June, 1912. At the same time, June 15, 1912, Pellagrin 162, a man 78 years old, the father of Pellagrin 152, suffered his initial erythema at his farm about three miles from Inman Mills. The intercourse between these two families was intimate, but the exact date of visits to the farm previous to the development of pellagra were not recorded. Inasmuch as the disease developed in Pellagrins 152 and 157 at nearly the same time, both of them have been assigned to Zone 3. The third case in Zone 3 in 1912 was Pellagrin

5. We hope to present the data in regard to seasonal relationships of pellagra in Spartanburg County in a subsequent paper. The largest number of initial attacks have appeared in the month of June and the largest number of recurrent attacks in the month of May.

150, a girl 16 years old, who came to Inman Mills in March, 1912. From March 13, 1912, to July 19, 1912, she boarded at 15 F Street and then moved with the same family to 5 A Street, where she developed her initial erythema about Aug. 1, 1912. She has been considered incident at 15 F Street, where her residence is indicated by a solid circle on the map, Figure 7, and her residence at 5 A Street has been indicated by a hollow circle. At 15 F Street her residence was next door to 13 F Street in which Pellagrin 163 resided until March 18, 1912. According to the rules of this study, this relationship of only five days cannot be considered. Pellagrin 150 left Inman Mills in September, 1912, and it has not been possible to interview her since that time. She has been assigned to the third zone.

The total population of Zone 3 in 1912, according to Table 12, numbered 687 persons. The three incident pellagrins in this group indicate an incidence rate of 0.44 per cent.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1913

A general survey of the map for 1913 (Fig. 8) shows a noticeable reduction in the number of incident cases in this year, as compared with 1912, a drop from sixteen to eight. The total number of old pellagrins in the mill, however, has increased from ten in 1912 to twenty-four in 1913. The number of old cases has been increased by the addition of most of the crop of cases incident in 1912. Twelve of these latter pellagrins have remained at Inman Mills, five of them suffering recurrence of symptoms in 1913, while the other seven escaped. There were twelve other pellagrins in whom the disease originated in an earlier year, or elsewhere in 1913. Five of these patients had resided at Inman Mills since 1912 or earlier, four of them suffering recurrence in 1913, while one escaped. The other seven were moved-in cases, five of whom showed active symptoms in 1913. These twenty-four cases have been indicated on the map for 1913, Figure 8, at their respective residences by the hollow circle, or by the hollow square if the disease was inactive in 1913. Several of these pellagrins changed their residences in 1913 and are designated at each house by the respective symbol.

Among the moved-in cases was Pellagrin 1253, who did not show initial symptoms until after her arrival in Inman Mills. She was a married woman, aged 25 years, who moved into 4 E Street on April 23, 1913. Just one week later, on May 1, 1913, her initial erythema appeared, so that she cannot be classed as incident at Inman Mills. Previous to her residence at Inman Mills, Pellagrin 1253 had lived for more than a year in another mill town where pellagra was very prevalent, and it is to this former residence that the origin of her disease has been ascribed. She has been indicated at 4 E Street by a hollow circle on the map for 1913, Figure 8.

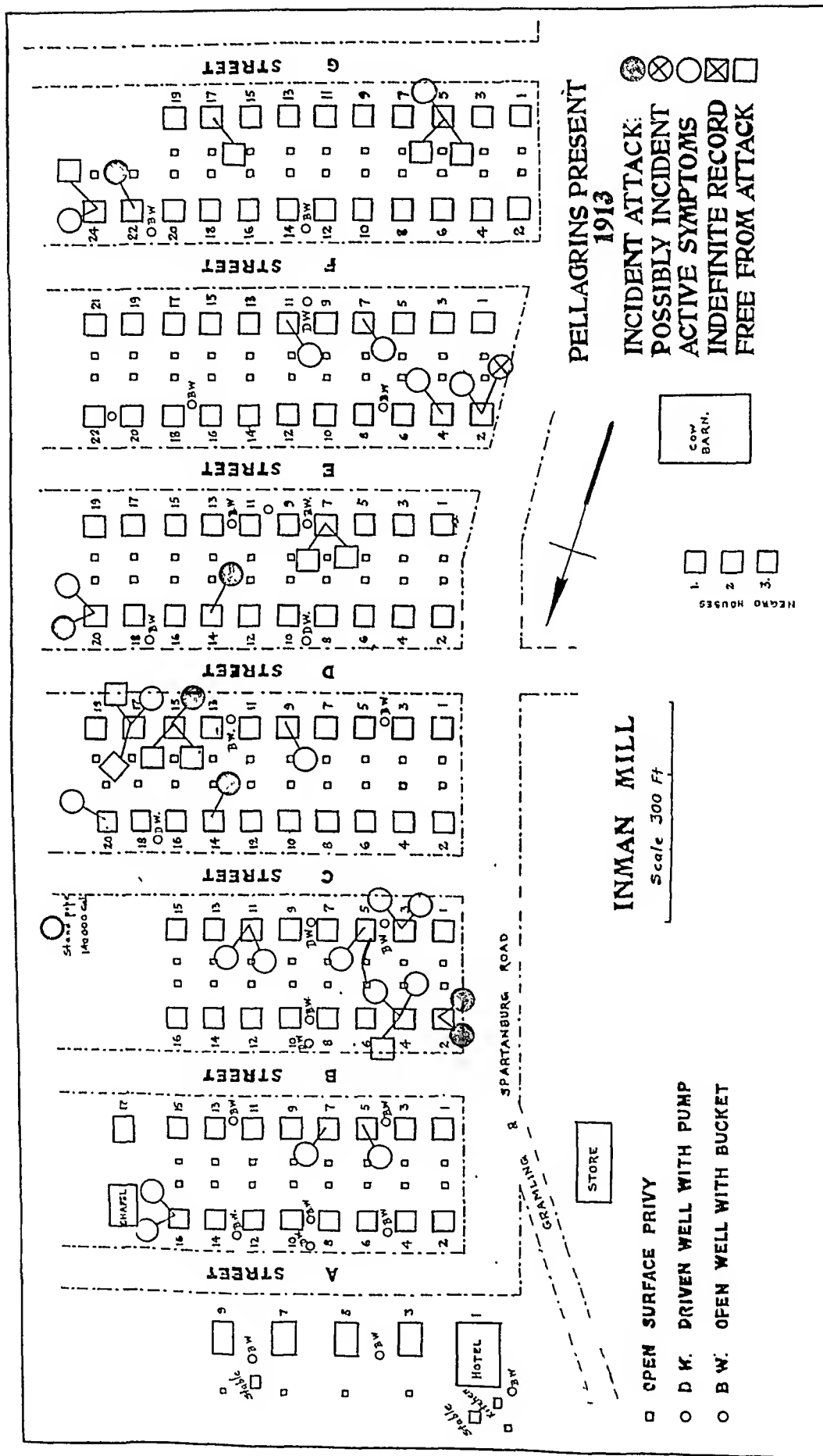


Fig. 8.—Map of Inman Mills, showing pellagrins present in 1913.

The data for the year 1913 are presented in Table 13. The data in regard to the eight pellagrins incident at Inman Mills in 1913 are briefly summarized in Table 7. Two of these new cases appeared in houses in which there was antecedent pellagra, while the remaining six originated in houses next door to antecedent pellagrins. No known cases of pellagra developed in persons living farther away than next door from a pellagrin in 1913. The first case in Zone 1, Pellagrin 588, a married woman aged 28 years, had lived at 15 D Street since Jan. 1, 1911. She was the mother of Pellagrins 148 and 149, the two little boys who contracted the disease in 1912. According to the statements of this woman, she had never had a pellagrous erythema until June, 1913, when the eruption was seen by us. Pellagrin 588 has been designated as incident in Zone 1 in 1913 and she has been indicated at 15 D Street by a solid circle on the map for 1913 (Fig. 8). Pellagrin 587,

TABLE 7.—PELLAGRINS INCIDENT AT DEFINITE HOUSES AT INMAN MILLS IN 1913

House	Residence in House	Zone	Residence in Zone	Onset Date	Pella-grin	Sex	Age
2B	Nov. 1, 1912 - Oct. 22, 1913.....	2	Nov. 1, 1912 - May, 1913....	May, 1913	559	F	24
2B	Since Jan. 11, 1913.....	2	Jan. 11, 1913 - May, 1913....	May, 1913	1059	F	21
14O	Since Dec. 16, 1912.....	2	July, 1912 - June 25, 1913....	June 25, 1913	589	F	32
14D	Mar. 1, 1913 - Apr. 1, 1913.....	2	Mar. 1, 1913 - Mar. 28, 1913..	Mar. 28, 1913	529	M	24
15D	Since Jan. 1, 1911.....	1	Since July 15, 1912.....	June, 1913	588	F	28
20D	Apr. 9, 1913 - June 20, 1913.....	2	Apr. 9, 1913 - May 2, 1913...	May 2, 1913	845	F	30
2E	Since Apr. 23, 1913.....	1	Since Apr. 9, 1913.....	May, 1913	587	F	31
22F	Since Nov. 15, 1911.....	2	Oct. 24, 1912 - June 15, 1913..	June 15, 1913	591	F	26

the second case designated as incident in Zone 1 in 1913, was a married woman 31 years old. She came to 2 E Street, Inman Mills, April 23, 1913. This house was arranged for two families, the other side of it being occupied at the time by Pellagrin 37. In the latter part of May, 1913, while residing in this house, Pellagrin 587 developed a definite erythema on the hands. According to the rules adopted for this study she has, therefore, been designated as incident in this house. When seen by us early in July, 1913, she reported that even before coming to Inman Mills, while at the house of Pellagrin 133 at Mill Village Sa, she had been troubled with sore mouth and diarrhea. Relying on the statements of this woman as to her history in the two or three weeks prior to her arrival in Inman Mills, it would seem justifiable to trace her incidence to the house of Pellagrin 133, where preliminary symptoms were observed. On the other hand, her residence at Inman Mills was in the same zone relationship as the earlier one, since Pellagrin 37 occupied the other side of the same house, and, inasmuch as the initial

erythema seems to have appeared after two weeks of residence here, 2 E Street, Inman Mills, has been designated as the house of origin. This has been done with considerable reservation, and on the map for 1913, Figure 8, this case has been indicated at 2 E Street by a circle containing a cross, because her incidence at this house is regarded as doubtful.

According to Table 13, the total exposed population in Zone 1 in 1913 numbered 118 persons, so that the appearance of two new cases would indicate an incidence rate of 1.69 per cent. for this zone in 1913.

Six of the incident pellagrins have been assigned to Zone 2. Pellagrins 559 and 1059 were two married women, aged 24 and 21 years, respectively, who were living in the same house at 2 B Street when they had initial attacks of pellagra at about the same time. Pellagrin 559 had moved into this house Nov. 1, 1912, coming from 21 F Street. Pellagrin 1059 had boarded at 5 A Street for about three months before moving to 2 B Street on Jan. 11, 1913. Neither had apparently lived near antecedent pellagra before her residence at 2 B Street, which was in next-door relationship to Pellagrin 164 at 4 B Street and to Pellagrins 160 and 161 at 3 C Street. Pellagrin 164 was incident in 1912, but had no recurrence of symptoms in 1913 or in 1914. The residence dates of Pellagrin 160 are rather uncertain for 1913, although it is probable that she spent some weeks in 1913 with her mother, Pellagrin 161, at 3 C Street. Pellagrin 161 is definitely known to have resided at 3 C Street until August, 1913, when she moved to 4 B Street; she suffered a recurrence in 1913. Pellagrins 559 and 1059 both developed the initial erythema at about the same time in May, 1913, and they have been designated as incident in Zone 2 at 2 B Street and are indicated there by solid circles on the map, Figure 8. Pellagrin 559 moved later in 1913 to 11 C Street, where she lived until March, 1914, when the family moved out of town. She has been designated at 11 C Street by a hollow circle on the map for 1913. The third case in Zone 2 was Pellagrin 589, a married woman 32 years old, who had an initial attack during the last week of June, 1913, at 14 C Street. According to the mill records, this family had lived at 13 F Street from May 6 until Dec. 15, 1912. Here they were in second-zone relationship to Pellagrin 280 from July, 1912. At 14 C Street, where they moved Dec. 16, 1912, they were again in the second zone, this time living next door to Pellagrins 148 and 149 and also next door to Pellagrin 588 after June, 1913. Pellagrins 148 and 149 were two little boys who were incident in 1912, but neither of whom showed any symptoms in 1913. Their mother, Pellagrin 588, had a definite attack in May or June, 1913. Pellagrin 589 has, therefore, been designated as incident in Zone 2 at 14 C Street and has been indicated by a solid circle at this house on the map for 1913, Figure 8. The fourth case in Zone 2 was Pellagrin

529, a man aged 24 years, who moved from Spartan Mills to Inman Mills late in February, 1913. He lived at 14 D Street from March 1 until the first of April, 1913. At Spartan Mills he had lived with his family at 175 Jennings Street since January, 1912. From March until May, 1912, Pellagrin 508, who had a severe recurrence in 1912, lived with them. Thereafter, so far as is known, no patient with pellagra resided in their vicinity until they came to 14 D Street March 1, 1913. This house was just across the street from Pellagrins 148 and 149 at 15 D Street. Here Pellagrin 529 developed a severe erythema about March 28, 1913, and he has been designated as incident here in the second zone and indicated by a solid circle at this house on the map, Figure 8. Immediately after the development of pellagra, this man left town with his family, going to the house of his father-in-law at Spartan Mills April 1, 1913. Within two months after his arrival his wife's parents both contracted the disease, the father-in-law dying in the summer of 1913. Pellagrin 529 left Spartan Mills in June, 1913, and went to Tennessee, where he died in September, 1913. The fifth case incident in the second zone in 1913 was Pellagrin 845, a married woman aged 30 years. According to the mill records, this woman lived at 20 D Street with her family from April 9, 1913, until June 20, 1913, when she left town and disappeared from record. Her initial erythema appeared on May 2, 1913, a little more than three weeks after her arrival at Inman Mills. Previous to this residence Pellagrin 845 had lived for nearly a year in another mill village conspicuous for its high incidence of pellagra, but the exact location of her residence there was not ascertained. At 20 D Street she was in next-door relationship to Pellagrins 145, 146 and 147 at 17 D Street. Pellagrin 145 had a recurrence in 1913, but Pellagrins 146 and 147, her two children, did not. Pellagrin 845 has been considered incident in the second zone in Inman Mills at 20 D Street and on the map for 1913, Figure 8, she had been indicated by a solid circle at this house. The sixth case incident in the second zone in this year was Pellagrin 591, a married woman aged 26 years, who had lived at 22 F Street since Nov. 15, 1911. This house had been vacated by Pellagrin 366 just before she moved in Oct. 24, 1912, Pellagrin 636 came to live next door at 24 F Street, remaining there until March 7, 1913. March 20, 1913, Pellagrin 592 moved into this house at 24 F Street. The erythema of Pellagrin 591 appeared about June 15, 1913. She has, therefore, been designated as incident in Zone 2 and has been indicated at 22 F Street by a solid circle on the map for 1913.

According to Table 13, the total exposed population in Zone 2 numbered 636 persons in 1913. The indicated rate of incidence for this zone was, therefore, 0.94 per cent.

There were no cases of pellagra found among the 594 persons living farther away than next door from an antecedent pellagrin in this year. The incidence rate for the third zone in 1913 was, therefore, zero.

THE DOMICILIARY RELATIONSHIP OF PELLAGRA IN 1914

An extensive canvass of Inman Mills was made in 1914, as in the two preceding years. Our field work covered the period from May 1 to Oct. 15, 1914. The data in regard to each house are briefly presented in Table 14. There were at Inman Mills in this year twenty-eight resident pellagrins who were incident in an earlier year, or elsewhere in 1914. Of these, nineteen showed active symptoms in 1914, six escaped recurrence, while for three the record for this year was indefinite. On the map for 1914, Figure 9, the nineteen pellagrins with active symptoms have been indicated at their respective residences by hollow circles. The six pellagrins who escaped recurrence have been designated by hollow squares at their respective residences, while the three cases with indefinite record have been indicated by squares containing a cross. When a pellagrin changed his residence during the year, he has been designated in a similar manner at each house. Among the pellagrins free from recurrence in 1914 were three who had not shown active symptoms for two years. These were Pellagrins 164, 148 and 149, all residents of Inman Mills, who had suffered only the one initial attack in 1912. These three cases appear on the map for 1914, Figure 9, and in Table 14, but have been excluded from consideration as potential centers of infection in 1914.

There were seventeen pellagrins whose incidence in 1914 has been traced to residence at Inman Mills. Seven of these cases appeared in houses in which an antecedent pellagrin had resided for a period of at least two weeks within six months prior to onset, nine arose among persons living next door to an antecedent pellagrin and one case was discovered in a family whose residence at Inman Mills was farther away than next door from an active pellagrin. The seventeen pellagrins incident in definite houses at Inman Mills have been designated at their respective residences on the map, Figure 9, by solid red circles. In several instances a pellagrin incident in one house moved to another house during 1914. Thus, Pellagrin 931, incident at 3 C Street, subsequently resided at 10 B Street, where her mother, Pellagrin 1079, came down with the disease. Later they both moved to 12 D Street and then again back to 3 C Street. Pellagrin 1081, incident at 11 D Street, moved to 4 C Street; Pellagrin 1286, incident at 13 D Street, moved to 3 C Street and Pellagrin 935, incident at 20 D Street, moved across the street to 19 D Street. At these respective subsequent residences each of these pellagrins is designated by a hollow circle on the map. These seventeen incident pellagrins are enumerated in Table 8.

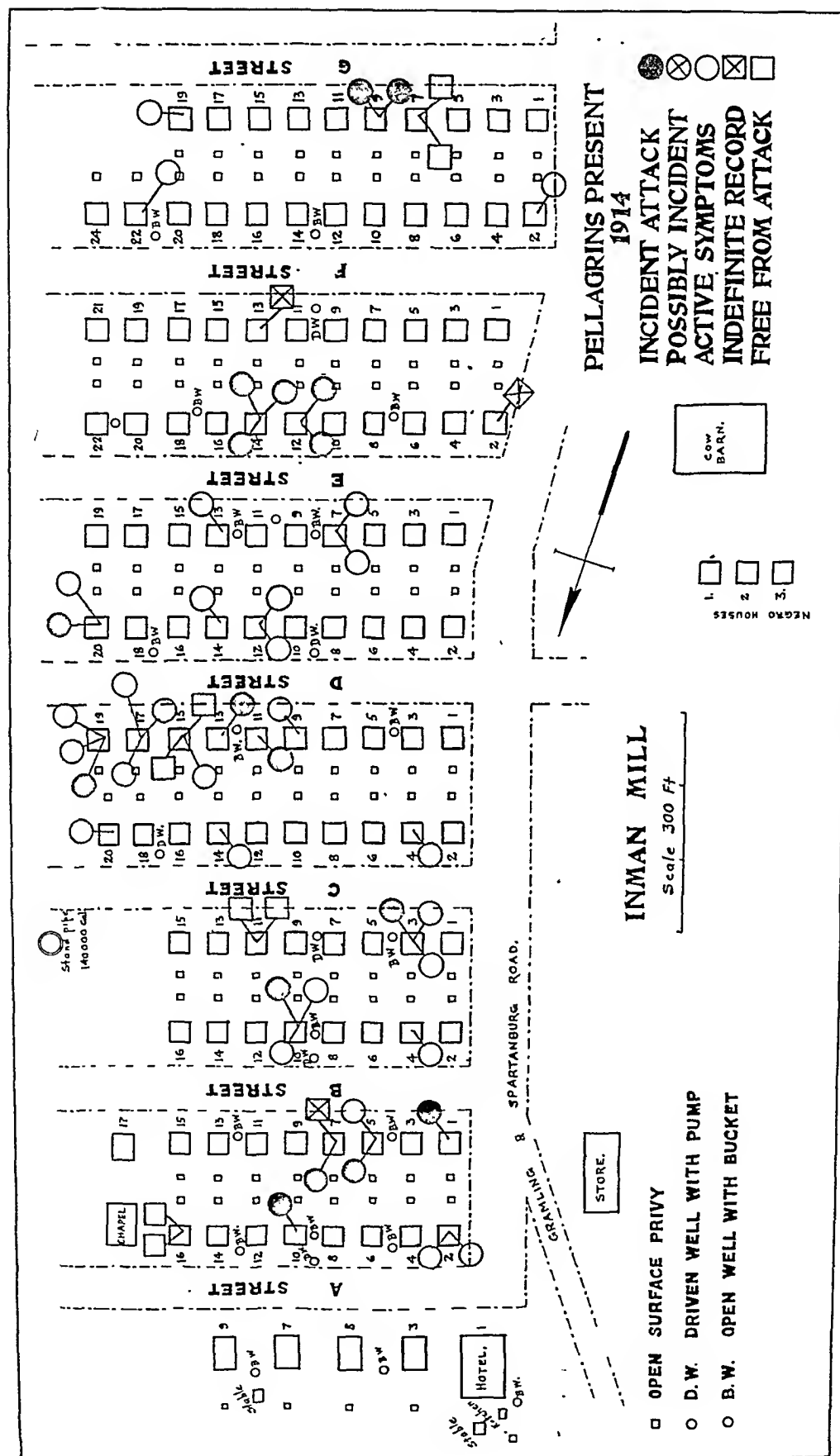


Fig. 9.—Map of Inman Mills, showing pellagrins present in 1914.

Seven cases have been assigned to Zone 1. Pellagrin 1080, a man 40 years old, the father of Pellagrin 114, had lived at 5 B Street since April 24, 1911. His daughter, who was living at home, suffered her initial attack in 1912 with recurrence in 1913 and 1914. Pellagrin 1080 developed his initial erythema in July, 1914. At 7 B Street Pellagrin 1077, a girl 3 years old, had lived with her mother, Pellagrin 883, since Dec. 1, 1913. The mother had her initial attack in 1911, escaped recurrence in 1912, suffered recurrence in 1913 and presented indefinite symptoms without erythema in 1914. The little girl developed her initial erythema about July 15, 1914. The third case in Zone 1, Pel-

TABLE 8.—PELLAGRINS INCIDENT AT DEFINITE HOUSES AT INMAN MILLS IN 1914

House	Residence in House	Zone	Residence in Zone	Onset Date	Pella-grin	Sex	Age
10A	Mar. 27 - May 28, 1914.....	2	Mar. 27, 1914 - May, 1914....	May, 1914	1129	M	9
1B	Since Jan. 16, 1910.....	2	June, 1912 - May 4, 1914....	May 4, 1914	930	M	62
5B	Since Apr. 24, 1911.....	1	Since July 1, 1912.....	Late July, 1914	1080	M	40
7B	Since Dec. 1, 1913.....	1	Since Apr., 1911.....	July 15, 1914	1077	F	3
10B	May 23, 1914 - June 27, 1914....	1	Since May 1, 1914.....	June 13, 1914	1079	F	32
3C	Aug. 6, 1913 - May 22, 1914....	2	Aug. 6, 1913 - May 1, 1914....	May 1, 1914	931	F	7
11D	Nov. 5, 1913 - Feb., 1914.....	2	Apr., 1912 - Feb., 1914.....	May, 1914	1081	F	11
13D	Dec. 12, 1913 - May 22, 1914....	2	Mar. 16, 1913 - May 15, 1914	May 15, 1914	1286	M	54
19D	Mar. 18, 1914 - July 25, 1914....	1	Since June, 1913.....	Apr., 1914	937	F	9
20D	Dec. 9, 1913 - Mar. 17, 1914.....	1	Since June, 1913.....	Late Mar., 1914	935	M	6
12E	Since Feb. 24, 1914.....	1	Since Apr. 1, 1914.....	Apr. 15, 1914	932	F	9
12E	Since Feb. 24, 1914.....	2	Jan. 15, 1914 - Apr. 1, 1914..	Apr. 1, 1914	933	F	6
14E	Since Feb. 10, 1914.....	2	Jan. 15, 1914 - May, 1914....	May, 1914	1247	M	4
14E	Since Feb. 10, 1914.....	2	Jan. 15, 1914 - May, 1914....	May, 1914	1248	M	6
14E	Since Feb. 10, 1914.....	2	Jan. 15, 1914 - May 15, 1914	May 15, 1914	1249	F	25
9G	Since Jan. 30, 1914.....	3	Jan. 30, 1914 - May 12, 1914	May 12, 1914	938	F	6
9G	Since Jan. 30, 1914.....	1	Since May 12, 1914.....	Late July, 1914	1078	F	42

lagrin 1079, was a woman 32 years old, whose little daughter, Pellagrin 931, had her initial erythema on May 1, 1914. The family lived at 3 C Street next door to Pellagrin 161 from Aug. 6, 1913, to May 22, 1914. They then moved to 10 B Street, where the mother's initial erythema appeared on June 13, 1914. She has been indicated as incident at 10 B Street, since she resided here for a period of three weeks prior to appearance of the erythema. In July, 1914, this family moved to 12 D Street, remaining there until August 15, when they returned to 3 C Street. The mother, Pellagrin 1079, has been classed as incident in Zone 1. The fourth case in Zone 1, Pellagrin 935, was a boy 6 years old. His family moved to 20 D Street, Inman Mills, late in 1913 and

moved from here to 19 D Street on March 17, 1914. His brother, Pellagrin 936, who was 3 years old, had his initial attack in June, 1913, before coming to Inman Mills, and suffered a recurrence in 1914. In March, 1914, soon after moving to 19 D Street, Pellagrin 935 developed his initial erythema, so that he has been classed as incident at the previous residence, 20 D Street. A few weeks later, in April, 1914, a third case of pellagra appeared in this family, Pellagrin 937, a sister 9 years old. She was the fifth incident case in Zone 1 in 1914, and has been designated as incident at 19 D Street. The sixth incident case in Zone 1, Pellagrin 932, was a girl 9 years old, who developed her initial erythema at 12 E Street April 15, 1914. Her sister, aged 6 years, Pellagrin 933, had suffered her initial erythema on April 1, 1914, so that the interval between the two cases was just two weeks. It is probable that both children acquired the disease at the same time and from the same source, but according to the rules adopted for this study the second case, Pellagrin 932, is classed as incident in Zone 1 in relation to her sister, rather than in Zone 2 in relation to the pellagrins next door to their house, namely, Pellagrins 549, 153 and 154. The two last mentioned were also little girls and playmates of Pellagrins 932 and 933. The seventh incident case in Zone 1 was Pellagrin 1078, a woman 42 years old, who had lived at 9 G Street since Jan. 30, 1914. Her daughter, Pellagrin 938, 6 years old, had developed pellagra May 12, 1914. The mother, Pellagrin 1078, had her first erythema in the last week of July, 1914. She was then in the seventh or eighth month of pregnancy and the attack of pellagra was mild, although she had a definite pellagrous eruption and sore mouth. Inasmuch as she had come to Inman Mills from a pellagrous neighborhood and had been pregnant since before her arrival, it is not improbable that the disease was actually contracted at her previous residence. Under the rules adopted for this study, however, she has been designated as incident in Zone 1 at Inman Mills in 1914.

The total number of exposed persons in Zone 1 in 1914, according to the data of Table 14, amounted to 163. The seven incident pellagrins in this zone indicate an incidence rate of 4.29 per cent. in 1914.

Nine incident pellagrins appeared in the population assigned to Zone 2. Pellagrin 1129, a boy 9 years old, moved to 10 A Street from Mill Village Ap March 27, 1914. He suffered his initial erythema in May, 1914, and the family moved back to their former residence May 28, 1914. This boy has been designated as incident in Zone 2 at 10 A Street. Pellagrin 930, a man 62 years old, had lived at 1 B Street since Jan. 16, 1910. He was not an ordinary factory worker, but held a better paid position of responsibility in the mill. No pellagrins had resided near him until 1912, in which year Pellagrin 164 developed the disease at 4 B Street. In 1913 pellagrins were living in two houses

just across the street from him, at 2 B Street and 4 B Street, and one of these, Pellagrin 161 at 4 B Street, remained during 1914. This man, Pellagrin 930, developed his initial erythema May 4, 1914, accompanied by diarrhea and general weakness. He remained away from his work until June 1. The third case in Zone 2, Pellagrin 931, a girl 7 years old, had lived with her parents at 3 C Street since Aug. 6, 1913. This house had just previously been vacated by Pellagrins 160 and 161, who moved to 4 B Street, immediately behind 3 C Street, where Pellagrin 161 remained during 1914, also. The little girl, Pellagrin 931, developed her initial erythema about May 1, 1914, at 3 C Street. The fourth case in the second zone, Pellagrin 1081, was a girl eleven years old, who had resided at 6 B Street from Nov. 15, 1911, to Aug. 31, 1913. The family then moved to 7 F Street, a house in the third zone, where they remained until Oct. 31, 1913. They then moved to 11 D Street, where they remained until February, 1914. This house was next door to Pellagrin 589 at 14 C Street during this entire period, and to Pellagrin 160 at 14 D Street after Jan. 15, 1914. In February the family moved to 4 C Street, where Pellagrin 1081 developed her initial erythema in May, about three months after the termination of the exposure at 11 D Street. The exact date of the appearance of erythema was not recorded in this case. If it appeared after May 15, the case would be designated as incident at 4 B Street, because Pellagrin 931, another little girl across the street at 3 C Street, had developed her initial erythema May 1, 1914. Although in this study we are adhering strictly to the rules adopted at the outset, it is nevertheless permissible to suggest that the relation of her home at 4 C Street to the very active pellagra focus at 3 C Street should be noted in passing. We have no idea as to how long before the appearance of the initial erythema an individual may be capable of disseminating pellagra, but it is doubtless a somewhat variable period. In this study, of course, no pellagrin is being considered as a possible center of infection until the date of the initial eruption. Pellagrin 1081 has, therefore, been designated as incident at the earlier residence, 11 D Street. The fifth case in Zone 2, Pellagrin 1286, was a man 54 years of age, who had lived next door to pellagrins since March 16, 1913. Dec. 12, 1913, he moved to 13 D Street, where he was next door to Pellagrins 588, 589, 148 and 149 in 1913 and 1914 and to Pellagrin 160, in addition, in 1914. He developed his initial erythema in this house May 15, 1914. A week later he moved to 4 C Street and Aug. 13, 1914, he moved away from Inman Mills. He died of pellagra about July 10, 1915, on a farm five miles from Inman Mills. The sixth case in Zone 2, Pellagrin 933, a girl 6 years old, had lived at 12 E Street since Feb. 24, 1914. Previously, this family resided at 15 E Street. At 12 E Street they were in next-door relationship to Pellagrins 549, 153 and 154. Pellagrins 153

and 154 were little girls, playmates of Pellagrin 933. The initial erythema appeared April 1, 1914, in this case. Pellagrin 932, sister of Pellagrin 933, also developed the erythema here April 15, and she has been discussed above in the group of cases developing in the first zone. The seventh, eighth and ninth cases in Zone 2 all developed at about the same time in May, 1914, at 14 E Street, so that no one of them can be regarded as antecedent to the others. They were Pellagrin 1249, a woman 25 years old, and her two sons, Pellagrins 1247 and 1248, aged 4 and 6 years, respectively. The family had lived at 11 E Street from Sept. 2, 1913, to Feb. 10, 1914, and were there in next-door relationship to Pellagrin 160 at 14 D Street from January 15 to February 10. They then moved to 14 E Street, a house in next-door relationship to Pellagrins 549, 592, 932 and 933. These two little boys played most of the day with the little girls at 12 E Street and at 7 E Street. The two boys and their mother developed the erythema about May 15, that is, four to six weeks after the little girls next door (Pellagrins 932 and 933) had shown the eruption. All three have been designated as incident in the second zone at 14 E Street.

According to Table 14, the total exposed population in Zone 2 numbered 586 persons in 1914. The nine incident cases, therefore, indicate an incidence rate of 1.54 per cent. for this zone in 1914.

One new case of pellagra appeared in a family living farther away than next door from an active pellagrin in 1914. This was Pellagrin 938, a girl 6 years old, who had lived at 9 G Street since Jan. 30, 1914. Next door to this house Pellagrin 164 lived at 7 G Street until March 10, 1914. She has, however, been excluded from consideration as a center of infection in this study in 1914, because she had not suffered an attack of pellagra since 1912. There was no other known case of pellagra in the immediate neighborhood of 9 G Street previous to the appearance of the erythema in Pellagrin 938. This little girl was an intimate playmate of the two little girls at 7 E Street, Pellagrins 153 and 154. Her erythema appeared on May 12, 1914, at about the same time that the other children who played with these girls were attacked by the disease (Pellagrins 932 and 933 at 12 E Street). Another possibility to be considered is that her mother, Pellagrin 1078, who has already been discussed above among the cases in Zone 1, may really have contracted pellagra before the family came to Inman Mills in January, 1914, and that the daughter may have acquired it from her. These are merely conjectures. The fact remains that this case, Pellagrin 938, has been designated as incident in Zone 3, in accordance with the rules adopted for this study.

According to Table 14, the total population in Zone 3 numbered 384 persons in 1914. The one case arising in this zone indicates an incidence rate of 0.26 per cent.

PELLAGRA AT INMAN MILLS SINCE 1914

Since the fall of 1914 we have not visited this mill village, and no complete house-to-house survey of it has been made, so far as we know. We are aware that some investigation was undertaken there in 1915 and in 1916 by the U. S. Public Health Service, and we had the pleasure of furnishing Professor Voegtlin a card index of the cases at Inman Mills on our records at the end of 1914. Exact information in regard to pellagra at Inman Mills in 1915 and 1916 is not at hand, but we know that this community has still continued to be an active focus of pellagra.

During our visits to Spartanburg City in August, 1915, and in August, 1916, complete lists were made of all pellagrins who had applied for treatment at the hospitals of the city, at the Pellagra Hospital of the U. S. Public Health Service and at the Pellagra Hospital provided by Spartanburg County at the County Farm. Our experience has shown that relatively only a small proportion of pellagrins are likely to apply for hospital treatment, especially during the initial attack, because of their reluctance to acknowledge the diagnosis, and inasmuch as Inman Mills is twelve miles from Spartanburg City, not many pellagrins could be expected to come to the city from that village. According to the records of these hospitals, Pellagrin 1403, the mother of Pellagrins 153 and 154, a woman 28 years old, with whom we became well acquainted at Inman Mills during 1912, 1913 and 1914, developed her initial attack of pellagra at 7 E Street in 1915; Pellagrin 1404, aged 5 years, another daughter of Pellagrin 1403, developed her initial attack in this same house in 1916; Pellagrin 1407, a married woman, had her first attack at a house on F Street in May, 1916, and Pellagrin 1435 also had her initial attack at Inman Mills in 1916, the location of her house not having been ascertained. All of these cases came to Spartanburg for treatment. There can be no doubt, therefore, that new cases of pellagra have continued to appear in the population of Inman Mills in the years subsequent to the termination of our epidemiologic study in that community.

COMMENT

The epidemiologic study of pellagra at Inman Mills, presented in the preceding pages, has been conducted under especially favorable circumstances, because this village had been recently built and occupied only since 1902. The records of the families occupying each house during the whole period of existence of the village have made it possible to ascertain the exact houses and the exact dates of occupancy for people who have been met with by us elsewhere in the county. As a result we feel confident that a large proportion, probably a majority,

of all cases of pellagra existing at Inman Mills previous to 1912 have come to our knowledge. Our own house-to-house surveys in 1912, 1913 and 1914 have been exceptionally thorough and complete in this community, and probably only very few recognizable pellagrins have escaped detection here in these years. The community is a more distinctly isolated unit than is Spartan Mills, and this has helped to keep the study simple. Furthermore, the same system of sewage disposal, namely, the open surface privy, continued to be used at Inman Mills throughout the period of our study.

The progressive extension of pellagra in this community seems to us to be a fact which cannot successfully be disputed. The number of pellagrins incident here in each year and the number of other active

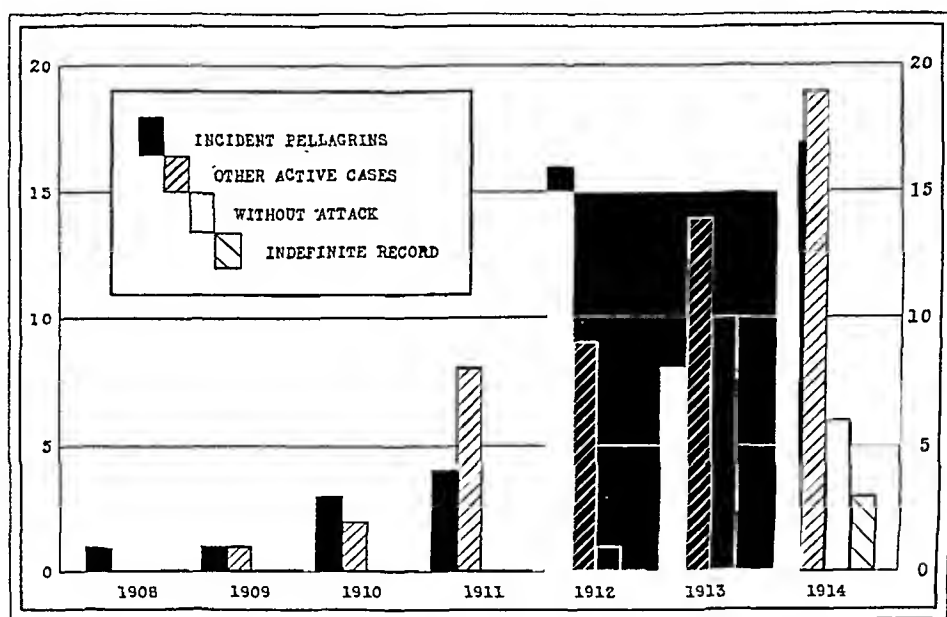


Fig. 10.—The number of pellagrins present in Inman Mills in each year from 1908 to 1914, inclusive. Pellagrins without attack were not observed here until 1912, when one such case was present. In 1914, three pellagrins with indefinite record were present.

pellagrins present are indicated in Table 9 and presented graphically in Figure 10. It is evident that pellagra was not a very prevalent disease at Inman Mills previous to 1911. Even in 1911 only four cases are known to have originated here. This year was one in which Spartanburg County, as a whole, experienced an enormous increase in pellagra. Our records⁶ have shown 234 incident pellagrins in the county in 1911 as compared with 141 in 1910 and 211 in 1912, and at Spartan Mills¹ there were twenty-two recognized incident cases in

6. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: The Incidence of Pellagra in Spartanburg County, S. C., and the Relation of the Initial Attack to Race, Sex and Age, *THE ARCHIVES INT. MED.*, 1916, **18**, 173.

1911, as against fourteen in 1910 and eight in 1912. Inman Mills, being off the main line of travel, evidently escaped to a large extent this increase of incident pellagra in 1911. In the latter part of 1911, however, the effects of the epidemic began to become evident at Inman Mills through the arrival of seven pellagrins, who had contracted the disease elsewhere (Fig. 6). One of these, Pellagrin 726, came to 18 F Street June 29, 1911, and moved away from the village again in September, 1911. Another, Pellagrin 163, came in September, 1911, to 13 F Street. Two others, Pellagrins 91 and 93 moved into 9 F Street in November, 1911, and from there to 8 A Street Dec. 31, 1911, and away from the village again March 27, 1912. A fifth, Pellagrin 145, moved in at 17 D Street in December, 1911, and a sixth, Pellagrin 514, came in December, 1911, to 1 A Street. The seventh, Pellagrin 328, came from Zone 1 in Spartan Mills, where she had manifested pre-

TABLE 9.—INCIDENT PELLAGRINS AND OTHER PELLAGRINS RESIDENT IN INMAN MILLS COMMUNITY IN EACH YEAR TO OCTOBER, 1914

	1908	1909	1910	1911	1912	1913	1914	Sum
Incident pellagrins	1	1	3*	4	10	8	17	50*
Other active pellagrins.....	0	1	2	8	9	14	19	53
Pellagrins without recurrence..	0	0	0	0	1	10	6	17
Pellagrins with uncertain record	0	0	0	0	0	0	3	3
Total active pellagrins.....	1	2	5*	12	25	22	36	103*
Total pellagrins present.....	1	2	5*	12	20	32	45	123*

* Including Pellagrins 198 and 883, who developed the initial erythema in 1911 within six months after moving away from Inman Mills and are, therefore, classed as possibly incident at Inman Mills in 1910.

monitory symptoms of pellagra, to 9 E Street on Nov. 16, 1911, developing her initial erythema at 9 E Street early in the spring of 1912. On April 1, 1912, these moved-in pellagrins were occupying the houses at 1 A Street, 17 D Street, 9 E Street and 13 F Street. Reference to the map for 1912, Figure 7, shows that of the sixteen persons who acquired pellagra at Inman Mills in 1912, no less than eleven contracted the disease while living in one of these identical houses or next door to one of them. The remarkable increase in new cases of pellagra at Inman Mills in 1912, following the epidemic in the county generally in 1911, would appear to have been caused largely by the influx of pellagrins into this somewhat segregated community at the end of 1911, whereby were provided four new centers for the spread of the disease, in which foci most of the new cases of 1912 appeared.

In 1913, on the other hand, the disease became distinctly less prevalent at Inman Mills, only eight new cases appearing, while at Spartan

Mills the new cases shot upward to thirty-one. In 1914, when Spartan Mills again improved, having only eighteen incident cases, Inman Mills suffered as severely as in 1912, having seventeen incident pellagrins in this year. When it is recalled that these two industrial communities are situated only twelve miles apart, that they are both engaged in the weaving of cotton cloth, both influenced alike by weather conditions, financial conditions, food conditions and industrial changes, it would appear impossible to explain the contrast which they present in respect to incidence of pellagra in different years by assuming that these variations have been due to variations in general prosperity or in the supply of food. On the other hand, a recognition of the fact that Spartan Mills is situated in the main business center of the county, on the main line of travel, and that Inman Mills is more segregated, off the beaten track, will suggest at once clearcut analogies to the mode of spread of other epidemic diseases.

The number of incident cases of pellagra at Inman Mills from 1908 to 1914, according to Table 9, has been fifty in a mean population of approximately 650 persons. No one will be able successfully to maintain that the causative factors of pellagra have not been operating in this mill village. It is, perhaps, worth while, therefore, to summarize these incident cases according to sex and age at onset of the disease, in order to show how characteristically the men in the age period from 15 to 44 have resisted these causative factors at Inman Mills. Such a summary is presented in Table 10. The three men in

TABLE 10.—DISTRIBUTION ACCORDING TO SEX AND AGE OF THE FIFTY PELLAGRINS INCIDENT AT INMAN MILLS, FROM 1908 TO 1914, INCLUSIVE

Age	0-14	15-29	30-44	Over 45	Age Un- known	Total
Females.....	9	14	9	1	0	33
Males.....	9	1	2	5	0	17

the age period 15 to 44 years in this table were Pellagrins 198, 529 and 1080, aged 41, 24 and 40 years, respectively, at the onset of the disease. Pellagrin 198 has also been included in the previous paper in this series as possibly incident at Spartan Mills. He was a chronic alcoholic. Pellagrin 529 said that he used whisky occasionally. The record of Pellagrin 1080 does not show whether he used alcohol or not. The occurrence of only three incident cases of pellagra in men from 15 to 44 years of age in this village during a period of seven years, while eighteen children under the age of 15 years, thirty-three women, aged from 15 to 44, one woman over 45 and five men over 45 years were

attacked by the disease, is quite in accord with the well-known relative insusceptibility of men in the active period of life.

The domiciliary relationship between old pellagrins and the newly incident cases seems to us to be the most significant feature of the pellagra situation at Inman Mills. The actual number of persons in

TABLE 11.—THE INCIDENCE OF PELLAGRA IN THE POPULATION IN EACH OF THE THREE DOMICILIARY ZONES AT INMAN MILLS IN 1912, 1913 AND 1914

Year	Zone 1			Zone 2			Zone 3		
	Exposed Population	Incident Cases	Incidence per Cent.	Exposed Population	Incident Cases	Incidence per Cent.	Exposed Population	Incident Cases	Incidence per Cent.
1912	129	6	4.65	587	7	1.19	687	3	0.44
1913	118	2	1.69	636	6	0.94	594	0	0.00
1914	163	7	4.29	586	9	1.54	384	1	0.26
Sum	410	15	3.66	1809	22	1.22	1665	4	0.24

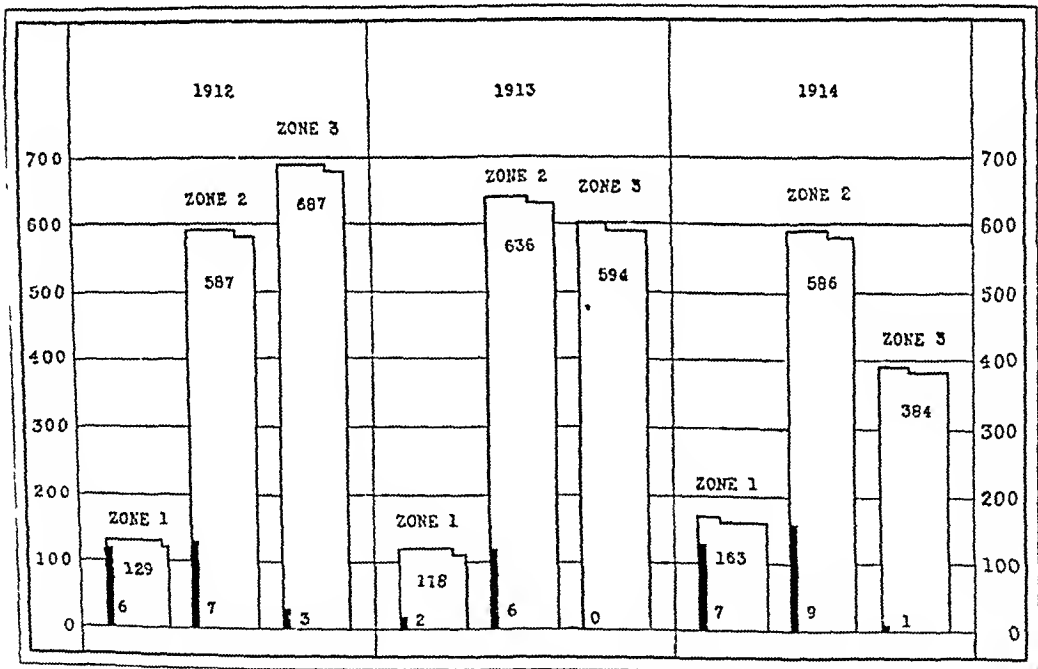


Fig. 11.—The total number of persons who were exposed in each of the three domiciliary zones in 1912, 1913 and 1914 is indicated by the area of the large columns. The included black column indicates in each instance the portion of the respective group which contracted pellagra.

each of the three zones of exposure for 1912, 1913 and 1914 is shown in summarized form in Table 11 and presented graphically in Figure 11. The incidence rates in each zone in each year are shown in Figure 12. During these three years 3.66 per cent. of the persons residing in Zone 1

contracted pellagra, 1.22 per cent. of the persons residing in Zone 2 contracted it and only 0.24 per cent. of the persons residing in Zone 3. In other words, living next door to a pellagrin has been associated with a five-fold increase in the danger of contracting pellagra as compared with living farther away in the same village, and living in the same house with a pellagrin has been associated with a fifteen-fold increase in this danger. A study of the maps accompanying this paper will show that this correlation has not been essentially due to the segregation of the pellagrous population in a particular part of the community,

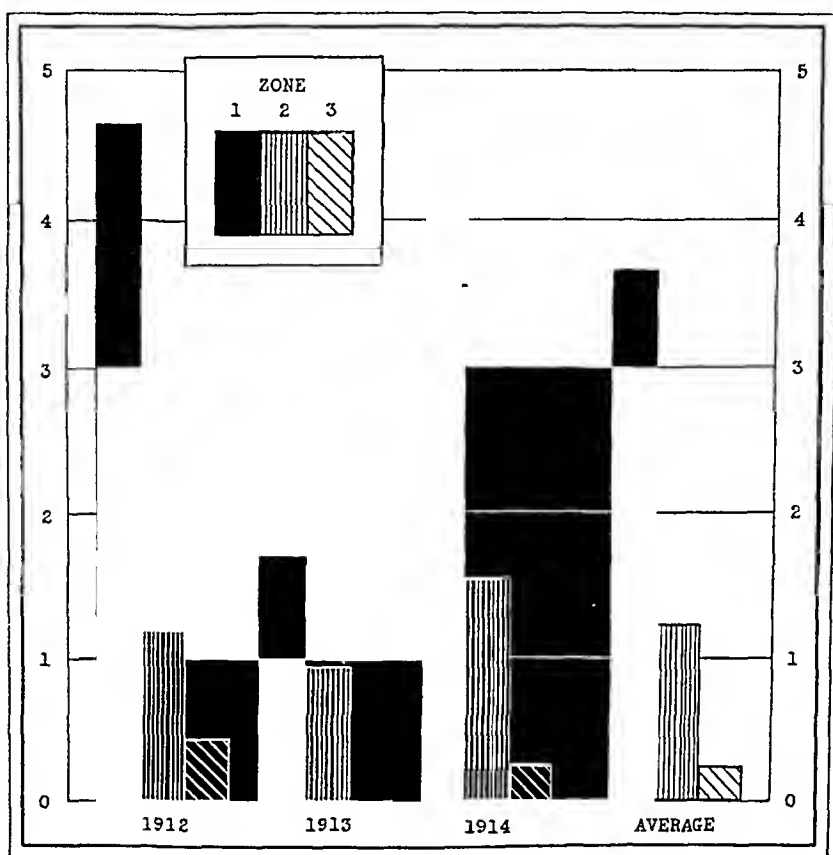


Fig. 12.—The black columns indicate the incidence rate of new cases of pellagra among persons living in the same house with a pre-existing case. The columns striped vertically indicate the incidence rate in the population living next door, and the columns striped obliquely indicate the incidence rate in the population living in the same village but farther away than next door from a pre-existing case of pellagra.

but that in each year there have existed separate distinct foci of pellagra in various parts of this village.

SUMMARY

1. Inman Mills is a cotton mill village of about 650 persons, situated in the country, relatively segregated from the main line of travel in

Spartanburg County. In several respects it presents a contrast to Spartan Mills, approaching more nearly the rural type of community in respect to water supply, sewage disposal, gardening, domestic animals and food supply.

2. This village remained relatively free from pellagra until after the great extension of the disease in Spartanburg County in 1911. In the following year there was a marked increase in the incidence of pellagra at Inman Mills in several very definite small foci, and since 1912 it has remained an active endemic center of the disease.

3. Men between 15 and 44 years of age have very largely escaped the disease here just as they have elsewhere in Spartanburg County.

4. In each of the three years of intensive epidemiologic study, the new cases of pellagra were found to have arisen almost exclusively in persons living in the same house with antecedent pellagrins, or next door to such houses.

5. In this community the spread of pellagra has evidently proceeded from the sick person to his healthy neighbors, either directly or indirectly through very limited distances.

6. Only a small percentage of the neighbors have been attacked in any year, and it is evident that susceptibility has been an important factor in this respect.

7. The relation of the spread of pellagra to the location of domicile at Inman Mills has been essentially the same as at Spartan Mills. These studies support the conclusions of our Second Progress Report in regard to the spread of pellagra.

TABLE 12.—DOMICILE RELATIONSHIP—INMAN MILLS—1912

1912	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ety- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
A Street										
1	514	1911	To June 25, 1912..... (Moved June)	5	1	Aug. - end 1912..... (New families)
2	118	1912	July 14 - Aug., 1912..... (New family; moved Aug.)	7	0	To Aug., 1912.....	12	0	Aug. - end 1912.....
3	113, 514, 113, 514, 315, 150	To Sept., 1912.....	5	0	Sept. - end 1912.....
4	113, 514, 150, 315, 114, 163	Entire 1912.....	5	0
5	150 315	1912 1912	Aug. 1 - Sept., 1912..... Aug. 20 - Sept., 1912	15	0	91, 93	To Mar. 27, 1912..... (Moved Mar.)	10	0	Mar. 27 - Aug. 1, 1912.. (New families)
6	91, 93	To Mar. 27, 1912..... (Moved Mar.)	2	0	Sept. - end 1912
7	114, 163, 150, 315	July - end 1912.....	2	0	Mar. 27 - July, 1912.... (New family)
8	91 93	1911 1911	To Mar. 27, 1912..... (Moved Mar.)	6	0	91, 93, 114, 163, 150, 315	To Mar. 27, 1912.....	6	0	Mar. 27 - Aug. 1, 1912.. Sept. - end 1912
9	152, 157	Aug. 1 - Sept., 1912	12	0	Mar. 27 - July, 1912.... (New family)
10	91, 93, 315, 150	June - end 1912..... To Mar. 27, 1912..... Aug. 1 - Sept., 1912	3 4	0 0	To June, 1912..... Mar. 27 - Aug. 1, 1912.. Sept. - Nov., 1912 (Moved Nov.; no further data)
12	Entire 1912.....
14	152	1912	152, 157	June - end 1912.....	2	0	To June, 1912.....
16	157	1912	5	0	To June, 1912.....
B Street										
1	164	June - end 1912.....	4	0	To June, 1912.....
2	160, 161, 164	Apr. - end 1912.....	6	0	To Apr., 1912.....
3	164, 114, 163	June - end 1912.....	3	0	To June, 1912.....
4	164	1912	June - end 1912.....	5	0	160, 161	Apr. - June, 1912.....	6	1	To Apr., 1912.....
5	114	1912	July - end 1912.....	7	0	91, 93, 164	To Mar. 27, 1912..... June - July, 1912	8	1	To Apr., 1912.....
6	163	1909	Summer, 1912	160, 161, 164, 114, 163	Apr. - end 1912.....	6	0	To Apr., 1912.....
7	91, 93, 114, 163	Mar. 9 - Mar. 27..... (No data to Mar.)	2	0	Mar. 27 - July, 1912....
8	114, 163	July - end 1912	4	0	To July, 1912.....
9	91, 93	July - end 1912	6	0	Mar. 27 - end 1912....
10	To Mar. 27, 1912.....	Entire 1912.....

[illegible]

TABLE 12.—DOMICILE RELATIONSHIP—INMAN MILLS—1912—(Continued)

1912	Zone 1					Zone 2		Zone 3				
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
D St. cont'd 12	328	1912	May - Nov. 26, 1912..... (New family; counted at 9 E; moved Nov.)	328	Spring - May, 1912.... (Moved away)	4	0	To spring, 1912..... Nov. 27 - end 1912..... (New family)	4	0
13	160, 328, 148, 149	To Apr., 1912..... May - end 1912	7	0		3	0
14	328, 148, 149	May - end 1912.....	9	0	To May, 1912.....	9	0
15	148 149	1912 1912	June - end 1912.....	6	0	145, 160	To June, 1912.....	8	2			
16	145, 146, 147, 148, 149	Entire 1912.....	5	0			
17	115 146 147	1904 1912 1912	Entire 1912..... Aug. - end 1912	6	2							
18	145, 146, 147, 148, 149	Entire 1912.....	17	1			
19	145, 146, 147	Entire 1912.....	12	0			
20	145, 146, 147	Entire 1912.....	21	0			
E Street	37	Entire 1912.....	27	0			
1	37	1908	Entire 1912.....	17	0	Entire 1912.....	12	0	Entire 1912.....	5	0
2	37	Entire 1912.....	4	0	To Apr., 1912.....	4	0
3	153, 154	Apr. - end 1912.....	Mar. - Dec., 1912..... (Moved; no further data)	3	0
4	Spring - Apr., 1912....	5	1	To spring, 1912.....	5	0
5	154 153	1912 1912	Apr. - end 1912..... June - end 1912	4	1	328	Apr. - end 1912.....	5	0	To Apr., 1912.....	5	0
6	153, 154, 328, 153, 154	May - July 15, 1912.... (New families; mov- ed July; no further data)	6	0			
7	328	1912	Spring - May, 1912..... (No data to spring; moved Apr. 30)	4	0	328, 153, 154, 280	Spring - July 15, 1912. New family; mov- ed July; no further data)	2	0	To spring, 1912..... (Moved away)	2	0
8	328	Spring - Nov. 26, 1912 (New family; mov- ed away)	6	0	To Jan. 31, 1912..... (Moved away)	2	0
9				Dec. - end 1912..... (New family)	2	0
10							
11							

TABLE 12.—DOMICILE RELATIONSHIP—INMAN MILLS—1912—(Continued)

1912	Zone 1					Zone 2		Zone 3		
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
D St. cont'd	328	1912	May - Nov. 26, 1912.... (New family; counted at 9 E; moved Nov.)	328	Spring - May, 1912.... (Moved away)	4	0	To spring, 1912..... Nov. 27 - end 1912..... (New family)
13	160, 328, 148, 149	To Apr., 1912..... May - end 1912	7	0	
14	328, 148, 149	May - end 1912.....	9	0	To May, 1912.....
15	148 149	1912 1912	June - end 1912.....	6	0	145, 160	To June, 1912.....	8	2	
16	145, 146, 147, 148, 149	Entire 1912.....	5	0	
17	145 146 147	1901 1912 1912	Entire 1912..... Aug. - end 1912	6	2					
18	145, 146, 147, 148, 149	Entire 1912.....	17	1	
19	145, 146, 149	Entire 1912.....	12	0	
20	145, 146, 147	Entire 1912.....	21	0	
E Street	147	Entire 1912.....	27	0	
1	37	1908	Entire 1912.....	17	0	37	Entire 1912.....	12	0	Entire 1912.....
2	Entire 1912.....	4	0	To Apr., 1912.....
3	153, 154	Apr. - end 1912.....	Mar. - Dec., 1912..... (Moved; no further data)
4	Spring - Apr., 1912....	5	1	To spring, 1912.....
5	154 153	1912 1912	Apr. - end 1912.....	4	1	328	Apr. - end 1912.....	5	0	To Apr., 1912.....
6	328	1912	Spring - May, 1912.... (No data to spring; moved Apr. 30)	4	0	153, 154, 328, 153, 154	May - July 15, 1912... (New families; mov- ed July; no further data)	6	0	
7	328, 153, 154, 280	Spring - July 15, 1912. New family; mov- ed July; no further data)	2	0	To spring, 1912..... (Moved away)
8	328	Spring - Nov. 26, 1912 (New family; mov- ed away)	6	0	To Jan. 31, 1912..... (Moved away)
9				Dec. - end 1912..... (New family)
10				
11				

12	163, 328 153, 161, 280 328	Entire 1912.....	7	0	0	Apr. 13 - May, 1912.... (No data to Apr.) Nov. 26 - end 1912	10	0
13	May - Nov. 26, 1912...	10	0	0	0
14	163, 328, 280	To May, 1912.....	6	0	0	Entire 1912.....	10	0
15	163	July - end 1912	12	0	0	Mar. 18 - end 1912....	7	0
16	To Mar. 18, 1912....	...	0	0	Entire 1912.....	9	0
17	0	0	Entire 1912.....	17	0
18	0	0	Entire 1912.....	17	0
19	0	0	Entire 1912.....	8	0
20	0	0	Entire 1912.....	19	0
22	0	0	Entire 1912.....	10	0
F Street	0	0	Entire 1912.....	9	0
1	37	Entire 1912.....	24	0	0	Entire 1912.....	11	0
2	37	Entire 1912.....	15	0	0	Entire 1912.....	8	0
3	0	0	To Dec., 1912.....	19	0
4	883	Dec. - end 1912.....	10	0	0	To Dec., 1912.....	11	0
5	0	0	To Dec., 1912.....	9	0
6	0	0	To Dec., 1912.....	18	0
7	0	0	To Dec., 1912.....	7	0
8	883	Dec. - end 1912.....	5	0	0	Mar. 13 - May 25, 1912. (Moved away)	5	0
9	280, 883	July - end 1912.....	20	0	0	To July, 1912.....	17	0
10	883	Dec. - end 1912.....	2	0	0	Apr. - July, 1912..... (New families)	10	0
11	163	To Mar. 18, 1912.....	6	0	0	Mar. 18 - July, 1912....	26	1
12	280, 883	July - end 1912.....	5	0	0	...	3	0
13	280	July - end 1912.....	14	1	0	Apr. - end 1912..... (No data to Apr.)	15	0
14	163	To Mar. 18, 1912.....	18	0	0	Mar. 18 - Sept. 30, 1912 (Moved; no further data)	10	0
15	280	July - end 1912.....	6	0	0	To Oct. 24, 1912.....	4	0
16	163	To Mar. 18, 1912.....	9	0	0	Entire 1912.....	9	0
17	163	(Moved Mar.)	...	0	0	To Oct. 24, 1912.....	11	0
18	280	To Mar. 18, 1912.....	...	0	0	To Oct. 24, 1912.....	5	0
19	July - end 1912	...	0	0	Feb. - Oct. 24, 1912.... (No data to Feb.)	13	0
20	163	Jan. 16 - Mar. 18, 1912	11	0	0	...	9	0
21	636	Oct. 24 - end 1912.....	9	0	0	Dec. - end 1912..... (No data to Dec.)	4	0
22	636	Oct. 24 - end 1912.....	5	0	0	Nov. - end 1912..... (No data to Nov.)
24	636	Oct. 24 - end 1912.....	...	0	0
Negro houses	0	0
1	0	0
2	0	0
3	0	0

TABLE 13.—DOMICILE RELATIONSHIP—INMAN MILLS—1913

1913	Zone 1					Zone 2			Zone 3			
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
A Street	Entire 1913.....	17	0
1	Entire 1913.....	12	0
2	Entire 1913.....	6	0
3	114	Entire 1913.....	5	0	...	6	0
4	Feb. 4 - end 1913..... (No data to Feb.)	6	0
5	5	0
6	114, 883	Entire 1913.....	9	0	Entire 1913.....	5	0
7	6	0
8	114, 883	Entire 1913.....	8	0	Jan. 16 - Dec., 1913....	6	0
9	152, 157	Dec. 1 - end 1913.....	6	0	Entire 1913.....	6	0
10	883
12
14	152, 157	Entire 1913.....	2	0
16	152 157	1912 1912	Entire 1913.....	5	0
B Street	160, 161, 164, 559, 1059	Entire 1913.....	4	0
1
2	559	1913	May - Oct. 22, 1913..... (Moved Oct.)	6	0	100, 161, 164	To May, 1913.....	5	2
3	1059	1913	May - end 1913.....
4	114, 160, 161, 164, 1059, 559	Entire 1913.....	3	0
5	164	1912	To July 29, 1913..... (Moved July)	5	0
6	161	1912	Aug. 1 - end 1913..... (New family; counted at 3 O)	8	0
7	160	1911	Entire 1913.....	114, 160, 161, 164, 883	Entire 1913.....	12	0
8	114	1912	114, 160, 161, 164, 883
9	114	To Nov. 29, 1913..... (Moved Nov.)	5	0
10	883	1911	Dec. 1 - end 1913..... (New family; counted at 5 O)	114, 883	Entire 1913.....	4	0	To Dec., 1913.....	6	0
11	833	Dec. - end 1913.....	6	0	To June 30, 1913.....	8	0
12	544, 559, 883	June 30 - July 21, 1913 Oct. 23 - end 1913	8	0	...	5	0
	Feb. 1 - end 1913..... (No data to Feb.)	5	0
	544, 559	June 30 - July 21, 1913 Oct. 23 - end 1913	7	0	To June 30, 1913.....	7	0

[illegible]

TABLE 13.—DOMICILE RELATIONSHIP—INMAN MILLS—1913 —(Continued)

1913	Zone 1				Zone 2				Zone 3			
	Ante- cedent Cause	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Cause	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
D Street												
1	Entire 1913.....	7	0
2	Entire 1913.....	12	0
3	Feb. 6 - end 1913.....	3	0
4	(No data to Feb.)		
5	Feb. 1 - end 1913.....	4	0
6	(No data to Feb.)		
7	8	0	Entire 1913.....	2	0
8	6	0	Entire 1913.....		
9	250	1912	Feb. 6 - end 1913..... (New family)	2	0	6	0	To Feb. 6, 1913.....	6	0
10	To Feb. 6, 1913..... (Moved Feb.)		
11	10	0			
12	11	0			
13	13	0			
14	10	0	To Feb. 6, 1913.....	2	0
	13	1			
15	148	1912	Entire 1913.....	7	1	2	0			
	149	1912	June - end 1913					
16	588	1913	6	0			
					
17	145	1904	Entire 1913.....	4	0	145, 146, 147, 148, 149, 588	Entire 1913.....					
	146	1912					
18	147	1912	10	0			
					
19	145, 146, 147, 845, 37,936	Entire 1913.....	12	0			

20	845	1913	May 2 - June 20, 1913.... (Moved June)	1	0	145, 146, 147	To May 2, 1913..... June 25 - Dec. 9, 1913.. (New families; mov- ed away)	21	1	0		
E Street												
1	845	1913	Dec. 9 - end 1913..... (New families; family of Case 936 not counted here for 1913)	2	0		Entire 1913.....	20	0	0		
2	37	1903	To Dec. 3, 1913..... (Moved Dec.)	12	1		May 1 - Aug. 26, 1913..	3	0	0	To May, 1913..... Aug. - end 1913	0
3	537	1913	May - end 1913.....	1253	To May 1, 1913..... Aug. 26 - end 1913	7	0	0		
4	1253	1913	May 1 - Aug. 26, 1913.... (New family; moved Aug.)	5	0	37, 537	Entire 1913..... To Jan. 31, 1913..... (Moved away)	1	0	0	Feb. 13 - May 1, 1913... (New family) Aug. 26 - end 1913	0
5	153, 154 883	May 1 - Aug. 26, 1913..	9	0	0		
6	1253	Entire 1913.....	6	0	0		
7	153 154	1912 1912	Entire 1913.....	4	0		Entire 1913.....	6	0	0		
8	153, 154, 883	Jan. 23 - end 1913.....	8	0	0		
9	153, 154, 280, 883	Entire 1913.....	4	0	0		
10	153, 154, 280	Entire 1913.....	0		
11	250	To Feb. 6, 1913..... (Moved Feb.)	0		
12	250	2	..	0		
13	0		
14	0		
15	0		
16	0		
17	845	May 2 - June 20, 1913..	2	0	0		
18	0		
19	845	May 2 - June 20, 1913..	5	0	0		
						936	Dec. 9 - end 1913.....	2	0	0		

TABLE 13.—DOMICILE RELATIONSHIP—INMAN MILLS—1913 —(Continued)

1913	Zone 1				Zone 2				Zone 3			
	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
				Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
E St. cont'd	Entire 1913.....	8	0
20	Entire 1913.....	23	0
F Street	37, 587, 1253	Entire 1913.....	10	0	Jan. 29 - Nov. 15, 1913. (Moved Nov.; no further data)	7	0
1			
2	37, 587, 1253	Entire 1913.....	23	0	To Oct. 1, 1913.....	12	0
3	(No further data)	9	0
4	883	To Jan. 31, 1913.....	10	0	Aug. 26 - end 1913.....	6	0
5	1253	May 5 - Aug. 26, 1913.. (New family)	5	0		16	0
6	565, 566, 567	Oct. 1 - Dec. 9, 1913....	6	0	To Oct. 1, 1913.....	8	0
7	883	1911	To Jan. 31, 1913..... (Moved Jan.; family of Case 883 counted at 5 O)	5	0	Dec. 9 - end 1913.....	9	0
8	883	To Jan. 31, 1913.....	12	0	Mar. 16 - end 1913..... (New families)	15	0
9	565, 566, 567	Oct. 1 - Dec. 9, 1913	9	0	Feb. - Oct. 1, 1913.....	5	0
10	883, 280	To Feb. 5, 1913.....	9	0	Dec. 9 - end 1913	5	0
11	280	1912	To Feb. 5, 1913..... (Moved Feb.; family of Case 280 counted at 9 D)	4	0	883	To Jan. 31, 1913..... (Moved away)	2	0	Feb. 6 - end 1913..... (New family)	9	0
12	Mar. 31 - end 1913..... (New families)	10	0
13	280, 883	To Feb. 5, 1913.....	5	0	Feb. 6 - end 1913.....	2	0
14	Feb. 6 - Mar. 31, 1913.. (Moved away)	6	0
15	280	To Feb. 5, 1913.....	2	0	Aug. 26 - end 1913..... (New family)	9	0
16	To Feb. 5, 1913.....	10	0	Feb. 6 - end 1913.....	12	0
				280	To Feb. 5, 1913..... (Moved away)	5	0	Entire 1913.....	10	0
				Feb. 6 - Mar. 8, 1913.. (New family; moved Mar.)	2	0
				636	Mar. 8 - May, 1913.... (New family)	3	0	May - end 1913.....	6	0

17	591	Nov. 8 - end 1913..... (New families)	8	0	To June, 1913..... (Moved away)	11	0
18	To Mar. 8, 1913..... (Moved Mar.)	11	0
19	636 592	To Mar. 8, 1913..... Mar. 20 - end 1913	14	0	Sept. 13 - end 1913..... (New family)	5	0
20	591	Mar. 8 - May, 1913.....	7	0	To Mar. 8, 1913.....	7	0
21	636 592	June - end 1913 To Mar. 7, 1913..... Mar. 20 - end 1913	13	0			
22	591	1913	June - end 1913.....	5	0	591	To Mar. 7, 1913..... Mar. 20 - June, 1913	6	1			
24	636	1911	To Mar. 7, 1913..... (Moved Mar.; family of Case 636 counted at 17 G)	6	0	592						
G Street	592	1911	Mar. 20 - end 1913..... (New family)	4	0							
1	Feb. 8 - end 1913..... (No data to Feb.)	1	0
3	Feb. 12 - Sept. 15, 1913 (No further data)	19	0
5	565 566 567	1911 1911 1912	Oct. 1 - Dec. 9, 1913..... (New family; not counted here for 1913; moved Dec.; no fur- ther data)	Mar. 26 - Sept. 15, 1913 (No data to Mar.; moved Sept.)	5	0
7	565, 566, 567	Oct. 1 - Dec. 9, 1913.....	4	0	Feb. 22 - Oct. 1, 1913..... (No data to Feb.)	14	0
9	Dec. 9 - end 1913 Feb. 21 - end 1913.....	3	0
11	(No data to Feb.)	3	0
13	Feb. 26 - end 1913..... (No data to Feb.)	9	0
15	636	Mar. 8 - May, 1913..... (No further data)	5	0	Feb. 28 - end 1913..... (No data to Feb.)		
17	636	1911	Mar. 8 - May, 1913..... (No data to Mar.; moved May)	4	0	May - end 1913..... (New family)	7	0
19	636, 591	Mar. 9 - end 1913..... (No data to Mar.)	9	0			
Negro	Entire 1913.....	9	0
houses	Entire 1913.....	4	0
1			
2			
3			

1911	Zone 1					Zone 2			Zone 3		
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
					Total	Incident Cases			Total	Incident Cases	
A Street	1	1353	1913	July 24, 1914 to date....	5	0	1252, 1253 930	July 24, 1914, to date.. May 4 - July 24, 1914...	8	0	To July 24, 1914.....
	2	1252	1914	1252, 1253	4	0	To May 4, 1914.....
	3	114, 930, 1252, 1253, 1080	July 24, 1914, to date.. Entire 1914 to date....	6	0	To July 24, 1914.....
	4	114, 930, 883, 1077 1129	5	0
	5	114, 1080, 883, 1077, 1129	Entire 1914 to date....	7	0	Entire 1914 to date....
	6	883, 1077 1129	Entire 1914 to date....	5	0	To May, 1914.....
	7	1129	May - May 28, 1914....	8	0	May 28, 1914, to date
	8	114, 1080, 883, 1077, 1129	Entire 1914 to date....	3	0
	9	1129	1914	May - May 28, 1914.... (Moved May)	7	0	152, 157 883, 1077	Entire 1914 to date.... To May, 1914.....	14	1
	10	1129	June 1, 1914, to date.. (New family)	4	0
B Street	12	152, 157	May - May 28, 1914....	4	0	To May, 1914.....
	14	152, 157	Entire 1914 to date....	2	0	May 28, 1914, to date
	16	152 157	1912 1912	Entire 1914 to date....	6	0	161 161, 930, 931, 1079, 1286	To May 4, 1914..... Entire 1914 to date....	5	1
	1	930	1914	May 4, 1914, to date....	4	0	1080, 161, 114, 930, 1080, 161, 1252, 1253	Entire 1914 to date....	11	0
	2	114, 161, 1080, 883, 1077, 931, 1286, 1079	Entire 1914 to date....	3	0
	3	114, 161, 1080, 883, 1077, 931, 1286, 1079	To Aug. 31, 1914..... (Moved Aug.; no further data)	6	0
	4	161	1912	Entire 1914 to date....	5	0	114, 883, 1059, 931, 1077, 1080, 1079	Entire 1914 to date....	4	0
	5	114	1912	Entire 1914 to date....	8	1	883, 931, 1077, 1059, 1079, 1129	Entire 1914 to date....	8	0
	6	1080	1914	July, 1914, to date....	883, 1077	Entire 1914 to date....	4	0
	7	883 1077	1911 1914	Entire 1914 to date.... July, 1914, to date....	8	1	114, 883, 1059, 931, 1077, 1080, 1079	July 22, 1914, to date.. (New family)	4	0
8	883, 1077	8	0
9	883, 1077	4	0
10	1059	1913	1913	To May 20, 1914..... (Moved May)	2	0	883, 1077	4	0
	931 1070	1914 1914	1914 1914	May 23 - June 27, 1914.. June 13 - June 27, 1914.. (New family; counted at 3 C for 1914; mov- ed June)	..	1*	883, 1077	4	0

11	1039, 931, 1079, 1129	To June 27, 1914.....	1	0	June 27, 1914, to date..	4	0
12	1039, 931, 539, 1079	To June 27, 1914.....	7	0	June 27, 1914, to date..	7	0
13	152, 157 559	Entire 1914 to date... To Mar. 10, 1914.....	1 10	0 0	Mar. 10 - Sept. 1, 1914... (Moved away; no further data)	4	0
15	152, 157	Entire 1914 to date....	6	0	Entire 1914 to date....	9	0
16	161, 931, 1079, 1081, 1286	Entire 1914 to date....	10	0			
O Street 1	931, 1081, 1079, 1256	May 1, 1914, to date...	13	0	To May 1, 1914.....	18	0
2	161	To May 1, 1914.....	8	1			
3	931	1914	May 1 - May 22, 1914... (Moved May)	161, 931, 1079, 1081, 1286	Entire 1914 to date....	6	0			
4	1286	1914	May 23 - Aug. 13..... (New family; moved Aug.)	6	0	931, 1079, 1031, 1256	May 1, 1914, to date...	3	0	To May 1, 1914.....	3	0
5	931	1914	Aug. 16, 1914, to date (Family counted above)	1059, 931, 1079	To June 27, 1914.....	9	0	June 27, 1914, to date..	6	0
6	1081	1914	May, 1914, to date.... (No data to May)	280	Entire 1914 to date....	5	0	June 27, 1914, to date..	3	0
7	559, 931, 1039, 1079	To June 27, 1914.....	3	0			
8	280, 539	Entire 1914 to date....	5	0			
9	539, 931, 1039, 1079	To June 27, 1914.....	6	0			
10	539, 931, 1039, 1079	Entire 1914 to date....	3	0			
11	559	1913	To Mar. 10, 1914..... (Moved Mar.)	2	0	559, 280, 589	To June 20, 1914..... (Moved June; no further data)	2	0			
12	164†	1912	539, 589	Aug. 31, 1914, to date. (New family)	3	0			
13	589, 588, 145, 146, 147	Entire 1914 to date....	3	0			
14	589	1913	To Aug. 21, 1914..... (Moved Aug.)	8	0	37, 145, 146, 147, 588, 935, 936, 937	Entire 1914 to date....	3	0			
15							
16							
18							
20	37	1908	Entire 1914 to date....	5	0							

* Indicates Pellagrin 1079, whose initial erythema appeared on June 13, 1914, three weeks after moving into this house. This residence, therefore, has been considered house of origin
† Pellagrins indicated in this manner are not considered centers of distribution in 1914.

1911	Zone 1				Zone 2				Zone 3				
	House Street and Number	Ante- cedent Case	First Ery- thema	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3	Exposed Population	
					Total	Incident Cases			Total	Incident Cases		Total	Incident Cases
D Street													
1	1081	May, 1914, to date....	6	0	To May, 1914.....	6	0
2	1081	Entire 1914 to date....	9	0
3	1081	May, 1914, to date....	3	0	To May, 1914.....	3	0
4	To Mar. 10, 1914.....	4	0
5	1081	May, 1914, to date....	2	0	(Moved Mar.; no further data)	2	0
6	153, 154	Entire 1914 to date....	5	0	To May, 1914.....		
7	280	Entire 1914 to date....	6	0			
8	153, 154, 280	Entire 1914 to date....	9	0			
9	280	1912	1912	To Sept. 15, 1914..... (Moved Sept.)	2	0							
10	280, 931, 153, 154, 1079	Entire 1914 to date....	5	0			
11	280, 160, 589	To Feb., 1914..... (Moved Feb.)	6	1			
12	931 1079	1914 1914	1914 1914	July 28 - Aug. 15, 1914... (New family; moved Aug.; counted at 3 C)	160, 280, 592	Feb., 1914, to date.... (New family)	3	0			
13	588, 589, 160, 931, 1079	Feb. 16 - June 30, 1914 (No data to Feb.)	3	0			
14	160	1911	1911		Sept. 1 - Sept. 14, 1914 (New family; mov- ed away)	2	0			
15	148 149 588	1912 1912 1913	1912 1912 1913	Jan. 15, 1914, to date.... Entire 1914 to date....	1 6	0 0		To May 15, 1914..... (Moved away)	7	1			
16		May 23, 1914, to date.. (New families)	7	0			
17	145 146 147	1904 1912 1912	1904 1912 1912	To June 19, 1914..... (Moved June)	4	0	160, 592, 588, 145, 146, 147	Entire 1914 to date....	3	0			
18	37, 588, 935, 936, 937	June 24, 1914, to date.. (New families)	6	0			
19	936 935 937	1913 1914 1914	1913 1914 1914	Mar. 18 - July 25, 1914... Late Mar. - July 25, 1914 Apr. - July 25, 1914 (New families; family of Cases 935, 936 and 937 counted at 20 D; moved July)	2	1	145, 146, 147, 588, 935, 936, 937	Entire 1914 to date....	7	0			
20	936	1913	1913	To Mar. 17, 1914..... (Moved Mar.)	8	1	37, 145, 146, 147, 936	To Mar. 16, 1914..... (Moved away)	2	0			
							145, 146, 147, 935, 936, 937	July 29, 1914, to date.. (New family)	2	0			
								Mar. 18 - July 25, 1914 (New families)	6	0			

TABLE 14.—DOMICILE RELATIONSHIP—INMAN MILLS—1914—(Continued)

1914	Zone 1				Zone 2			Zone 3		
	Ante- cedent Case	First Ery- themn	Time in Zone 1	Exposed Population		Ante- cedent Case	Time in Zone 2	Exposed Population		Time in Zone 3
				Total	Incident Cases			Total	Incident Cases	
F St. cont'd										
12	519	1913	Feb. 28 - Aug. 7, 1914... (New family; moved Aug.; no further data)	9	0	938, 1078	May 12, 1914, to date...	4	0	To May 12, 1914.....
13								To Feb. 15, 1914..... (Moved away)
14						549	Feb. 28 - Aug. 7, 1914...	9	0	To Feb. 28, 1914.....
15						549, 1247, 1248, 1249	Feb. 28 - June 30, 1914 (New families; mov- ed June; no fur- ther data)	5	0	To Feb. 28, 1914..... (Moved away)
16						549	Feb. 28 - Aug. 7, 1914...	9	0	To Feb. 28, 1914.....
17								Mar. 15 - Aug. 31, 1914 (No data to Mar.; moved Aug.; no further data)
18						549, 591	Mar. 10, 1914, to date. (New family)	5	0	To Feb. 28, 1914..... (Moved away)
19						591	To Mar. 6, 1914.....	6	0	Mar. 6, 1914, to date...
20						591	Jan. 19, 1914, to date...	13	0	
21						591	To Mar. 6, 1914.....	3	0	
22	591	1913	To Mar. 6, 1914..... (Moved Mar.; family of Case 591 counted at 19 G)	2	0	591	Mar. 6, 1914, to date...	5	0	Mar. 6, 1914, to date...
24						591	To Mar. 6, 1914.....	4	0	Mar. 6, 1914, to date...
G Street										
1						934	May 15 - July 24, 1914	4	0	To May 15, 1914.....
3						934	May 15 - July 24, 1914 (No data to May)	6	0	
5	164	1912				559	Aug. 8, 1914, to date...	8	0	To Aug. 8, 1914.....
7	559	1913	Aug. 8, 1914, to date... (New family; counted at 11 O)			938, 1078	May 12 - July 31, 1914 (Moved July)	7	0	To May 12, 1914..... (Family of Case 164 not counted here)
9	938	1914	May 12, 1914, to date...	7	1			To May 12, 1914.....
11	1078	1914	July, 1914, to date			938, 1078	May 12, 1914, to date.	4	0	To May 12, 1914.....
13								Entire 1914 to date...
15						591	Mar. 7, 1914, to date...	6	0	Entire 1914 to date...
17						591	To Mar. 6, 1914..... (Moved Mar.)	9	0	To Mar. 7, 1914.....
19	591	1913	Mar. 7, 1914, to date... (New family)	3	0			
Negro houses										
1								Entire 1914 to date...
2								Entire 1914 to date...
3								Entire 1914 to date...

THE ABSORPTION OF PHENOLSULPHONEPHTHALEIN FROM THE SUBARACHNOID SPACE IN DIS- EASES OF THE CENTRAL NER- VOUS SYSTEM*

HENRY G. MEHRTENS, M.D., AND HOWARD F. WEST, M.D.
SAN FRANCISCO

Since 1842 various observers, beginning with Magendie, have demonstrated that pigments injected into the subarachnoid space eventually appear in the urine. Dandy and Blackfan¹ were the first to apply this knowledge to the study of pathologic conditions. They showed that phenolsulphonephthalein injected into the subarachnoid space is harmless and appears in the urine in normal infants in from four to ten minutes. Their studies were confined to hydrocephalus in infants and to certain animal experiments. As a result of these observations they were led to conclude that there is an active circulation of the spinal fluid; that it is constantly absorbed; and that absorption takes place directly into the vascular supply of the whole subarachnoid space. So far as we know, no other pathologic studies have been made in this way. Cushing and Weed,² using the same dye in connection with their work on the spinal fluid, were convinced that absorption takes place largely by way of the subarachnoid villi into the cerebral sinuses. Motte and Nageotte³ believe that there may be considerable absorption of the spinal fluid by way of the perineural lymphatics.

The following observations were made to determine, if possible, whether there might be some disturbance in the excretion of phenolsulphonephthalein in diseases of the central nervous system other than hydrocephalus. The method adopted consisted, in brief, of doing a lumbar puncture, injecting 1 c.c. of neutral phenolsulphonephthalein,¹ catheterizing the patient and timing the appearance of the dye in the urine.

Certain practical points were soon evident, both from the standpoint of accuracy in results and in maintaining aseptic conditions. In the first place it was noted that there was a tendency for the dye to be

* Submitted for publication May 22, 1917.

* From the Division of Medicine, Leland Stanford, Jr., University Medical School.

1. Dandy and Blackfan: Internal Hydrocephalus. *Am. Jour. Dis. Child.*, 1914, **8**, 406.

2. Cushing and Weed: Studies on the Cerebrospinal Fluid. *Jour. Med. Research*, 1914, **31**, 1.

3. Nageotte and Riche: Tabes Dorsalis. *Manuel d'Histologie Pathologique*. Cornil and Ranvier, Ed. 3, 1907.

distributed along the path of the needle after withdrawal, giving ample time for it to be absorbed in considerable concentration from the subcutaneous tissues. This would allow it to appear in the urine in practically all cases in ten minutes or less, and would obscure the actual appearance from the subarachnoid space. To overcome this tendency it was found practicable to withdraw 2 or 3 c.c. of spinal fluid in a sterile syringe to be reinjected following the phenolsulphonephthalein so as to leave only clear spinal fluid in the needle. In order that 1 c.c. of phenolsulphonephthalein should replace exactly 1 c.c. of spinal fluid, the following method was devised. This, while extremely simple, was quite as satisfactory as the complicated apparatus with stop-cocks, etc., devised for lumbar puncture that one may find on the market.

The method consists of a needle and syringe adapter joined by three quarters of an inch of small rubber tubing. The first connects with the puncture needle, the latter exactly fits the Luer syringes. When the needle enters the subarachnoid space the obturator is withdrawn and the connecting piece, held with a clamped artery forceps which closes the rubber tubing, is immediately slipped into place. One can then at his leisure attach the manometer for reading the pressure or can withdraw exact amounts of fluid by gradually opening the clamp. Having read the pressure and withdrawn 1 c.c. of fluid to be discarded and 3 c.c. to be held in reserve, exactly 1 c.c. of the neutral phenolsulphonephthalein is slowly injected followed by the 3 c.c. of fluid previously withdrawn. The time of injection is noted. Before withdrawing the needle the patient's legs are slowly straightened (the lateral position is used) so that the changed tissue planes tend to prevent any escape of fluid and phenolsulphonephthalein. Great care should be taken in withdrawing the fluid not to exert suction, the intradural pressure being allowed to push back the piston of the syringe unassisted. It is also well, before introducing the phenolsulphonephthalein, to dilute it by allowing 2 or 3 c.c. of fluid to enter the syringe and then slowly to inject the whole. Obviously the strictest aseptic precautions must be observed at every step of the procedure.

Following the injection, the patient is catheterized and the urine allowed to drop into a series of test tubes containing small amounts of sodium hydroxid. These are placed in order in a rack and the time of drawing off each is noted. The first tube to show a definite pink color is an indicator of the excretion time. On the following day, provided the phenolsulphonephthalein has disappeared from the urine, 1 c.c. is injected intramuscularly according to the usual technic for kidney function test, and the time of the appearance in the urine noted. Practically, it is rarely necessary to catheterize the patient on this examination, merely having him void at the end of ten minutes, at which time the dye is in most cases present in the urine. This, with careful urine analysis, was done to rule out any delays due to kidney disease.

Quantitative estimations were made in a considerable number of cases, but these were found to vary so greatly as to be of little value. The dye is apparently absorbed very slowly from the subarachnoid space and in many instances may suffer considerable reduction before complete elimination can take place.

Apparently the observations reported by Kendall⁴ had not been

4. Kendall: The Fate of Phenolsulphonephthalein When Injected Into the Animal Organism, *Jour. Am. Med. Assn.*, 1917, 68, 343.

extended to include the cerebrospinal fluid. A series of fluids were therefore tested for their reducing ability. Eighteen different fluids were incubated with measured quantities of phenolsulphonephthalein for varying lengths of time. Some of these showed a reduction of from 10 to 20 per cent., others no reduction whatever. While there are certain features about this reduction (percentage) that have not yet been explained, it is safe to say that the decrease in the recoverable dye is not sufficiently great to interfere with qualitative tests.

The series discussed below consists of fifty-nine individuals who were selected from the neurologic and medical clinics of Stanford University Medical School so as to include a reasonable number of supposedly normal persons (neurologically), the others representing as great a variety as possible of organic central nervous system diseases. The series may be divided into five groups.

Group I includes twelve persons whose symptomatology, physical signs and spinal fluid analyses suggested no organic disease of the central nervous system or disease of the urinary tract. These are shown in the table. It will be observed that this group contains persons ranging in age from 27 to 54 years. While it is probable that old age, especially when associated with considerable arteriosclerosis, tends to prolong the appearance time, still the results in this group may be taken as fairly well representing the normal appearance. The time in this series averages practically nine minutes. In these individuals there is no apparent relationship between age and appearance time, neither can a definite relationship between spinal fluid pressure and appearance time be established.

Group II is definitely pathologic. It includes thirty-one persons having both physical and laboratory evidence of organic central nervous system disease. Of this number thirty were syphilitics, nine having been diagnosed tabes dorsalis, five paresis, one juvenile paresis, eleven cerebrospinal syphilis, one pachymeningitis hypertrophica cervicalis syphilitica, one Erb's spastic paraplegia, one syphilitic amyotrophic lateral sclerosis, one gumma of parietal bone with meningeal involvement. The other case was one of tuberculous meningitis. In this group the appearance time ranged from five to seventy-four minutes. In tabes the appearance time ranged from fifteen to sixty minutes, with one exception it was thirty minutes or over, averaging forty-two minutes. Again, one finds no direct relationship between the length of the appearance time and the age, but in this group the average spinal fluid pressure was definitely increased. The five paretics ranging from eighteen to fifty minutes, with one exception, all ran thirty minutes or over, averaging thirty-eight minutes. In this group there was more of a correspondence between age and appearance time.

TABLE SHOWING ABSORPTION OF PHENOLSULPHONEPHTHALEIN FROM THE SUBARACHNOID SPACE IN VARIOUS—
Group I.—Individuals Having Neither Physical Nor Laboratory Evidence of Organic Disease of the Central Nervous System.

Number	Age	Clinical Diagnosis	Phthalein Ap- pearance Time		Wassermann		Spinal Fluid Analysis				Colloidal Gold Reaction (Lange)
			Intra- spinal, Min.	Intra- muscular, Min.	Blood	Spinal	Pres- sure, Mm.	Nonne	Noguchi	Cells	
3128	27	Gastritis.....	7	Under 10	100	+	1	0000000000
3471	26	Constipation.....	5	Under 10	170	2	1000000000
3528	30	Normal.....	10	Under 10	120	1	0000000000
1669	52	Normal.....	10	Under 10	110	+	+	2	0000000000
3098	24	Mediastinitis.....	14	Under 10	130	1	0000000000
7225	29	Normal.....	10	Under 10	150	1	1100000000
3110	50	Broken nose.....	10	Under 10	150	2	1110000000
3044	57	Manic depressive.....	5	Under 10	90	2	0000000000
3029	26	Neurasthenia.....	6	Under 10	100	1	0011000000
3048	41	Epilepsy.....	4	Under 10	120	1	0000000000
3080	31	Manic depressive.....	6	Under 10	130	1	0000000000
3048	33	Normal.....	7	Under 10	150	+	1	0110000000

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease

2163	29	Tabes dorsalis.....	30	6	+++	+++	200	+++	+++	30	1222332000
7034	51	Tabes dorsalis.....	45	7	+++	+++	230	++	++	11	2233320000
3842	26	Tabes dorsalis.....	55	5	+++	+++	150	++	+	50	1221100000
1850	37	Tabes dorsalis.....	15	4	+++	210	++	+	26	1233310000
7133	47	Tabes dorsalis.....	34	10	+++	+++	250	++	++	74	0122110000
3495	45	Tabes dorsalis.....	42	7	+++	+++	310	+++	+++	34	2234310000
3882	35	Tabes dorsalis.....	55	6	+++	165	++	+	44	3332210000
3400	44	Tabes dorsalis.....	60	10	+++	180	+	+	12	1123320000
3336	40	Tabes dorsalis.....	40	6	+++	190	+	+	86	1123100000
1057	52	Paresis.....	52	6	+++	+++	270	+	+	28	1110000000
.H. 1	46	Paresis.....	43	8	+++	+++	200	+++	+++	22	555554433
.H. 2	28	Paresis.....	18	7	+++	+++	190	+++	+++	75	555554332
.H. 3	40	Paresis.....	32	7	+++	+++	210	++	++	50
1157	34	Paresis.....	45	5	+++	+++	200	+++	+++	150	5544400000
3870	10	Juvenile paresis.....	23	5	+++	+++	140	+++	+++	42	5333200000
3057	25	Cerebrospinal lues.....	45	7	+++	+++	170	+++	+++	48	3333200000
5220	33	Cerebrospinal lues.....	25	11	+++	+++	200	+++	+++	160	1223321000
3523	46	Cerebrospinal lues.....	74	5	++	+++	190	+++	+++	33	2234320000
3719	23	Cerebrospinal lues.....	26	4	+++	+++	150	+++	++	56	3444400000
3884	44	Cerebrospinal lues.....	65	6	+++	+++	150	++	+++	45	1112232000

—GROUPS OF NORMAL PERSONS AND PERSONS WITH DISEASE OF THE CENTRAL NERVOUS SYSTEM

Group I.—Individuals Having Neither Physical Nor Laboratory Evidence of Organic Disease of the Central Nervous System

Urine	Subjective Symptoms	Physical Signs					
		Eyes	Knee Jerk	Ankle Jerk	Bladder	Dysarthria	Ataxia
Trace alb.	Pain in the epigastrium.....	Normal	Normal	Normal	Normal	None	None
Normal	Nervousness	Normal	Normal	Normal	Normal	None	None
Normal	Worry	Normal	Normal	Normal	Normal	None	None
Normal	Normal	Normal	Normal	Normal	None	None
Normal	Pain in the chest.....	Normal	Normal	Normal	Normal	None	None
Normal	Normal	Normal	Normal	Normal	None	None
Normal	Headache.....	Normal	Normal	Normal	Normal	None	None
Normal	Flight of ideas.....	Normal	Normal	Normal	Normal	None	None
Normal	Palpitations.....	Normal	Normal	Normal	Normal	None	None
Normal	Epileptic attacks	Normal	Normal	Normal	Normal	None	None
Normal	Depression.....	Normal	Normal	Normal	Normal	None	None
Normal	Normal	Normal	Normal	Normal	None	None

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease

Normal	Gastric crises; pains in the legs....	Pupils unequal; fixed to light	Absent	Absent	Normal	None	Present
Normal	Poor vision; pains in the legs....	Pupils fixed; optic atrophy	Present	Present	Incontinence	None	Sh
Normal	Poor vision; pains in legs and arms	Pupils unequal; fixed; optic atrophy	Present	Absent	Normal	None	Sh
Normal	Paresthesias in arms and legs....	Pupils unequal; fixed	Absent	Absent	Normal	None	Present
Normal	Photophobia; pains in legs; impotency	Pupils unequal; fixed	Present	Present	Normal	Slight	Ab
Normal	Paresthesias; pains in the legs....	Pupils unequal; fixed; irregular	Absent	Absent	Dribbling	None	Present
Normal	Pains in legs; severe gastric crises	Pupils sluggish	Absent	Absent	Normal	None	Ab
Normal	Shooting pains in legs; trophic ulcer	Pupils fixed	Present	Present	Normal	None	Sh
Trace alb.	Pains in legs; difficult urination...	Pupils sluggish	Absent	Absent	Dribbling	None	Present
Normal	Euphoric; elated; grandiose.....	Pupils unequal	Exaggerated	Exaggerated	Normal	Slight	Ab
Normal	Euphoric; partially demented.....	Pupils fixed	Increased	Increased	Normal	Present	Sh
Normal	Euphoric; violence	Pupils unequal; fixed	Increased	Increased	Incontinence	Present	Present
Normal	Demented	Pupils unequal; fixed	Increased	Increased	Incontinence	Present	Present
Normal	Irritability; headaches	Pupils sluggish	Increased	Increased	Incontinence	Present	None
Normal	Spastic paralysis; mental retrogression	Pupils fixed	Increased	Increased	Dribbling	Present	Sh
Normal	Headache; diplopia	Iritis	Increased	Increased	Normal	None	None
Normal	Headache; vertigo; paresthesias...	Pupils unequal	Increased	Increased	Normal	None	Present
Normal	Depression; paresthesias	Pupils sluggish	Increased	Increased	Normal	None	None
Normal	Depression; paresthesias; headache	Unequal; sluggish; irregular pupils	Absent	Absent	Normal	None	None
Normal	Vertigo; pains in legs.....	Normal	Increased	Increased	Dribbling	None	None

TABLE SHOWING ABSORPTION OF PHENOLSULPHONEPHTHALEIN FROM THE SUBARACHNOID SPACE IN VARIOUS—

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease.—(Continued)

Number	Age	Clinical Diagnosis	Phthalein Ap- pearance Time		Wassermann		Spinal Fluid Analysis				Colloidal Gold Reaction (Lange)
			Intra- spinal, Min.	Intra- muscular, Min.	Blood	Spinal	Pres- sure, Mm.	Nonne	Noguchi	Cells	
581	44	Cerebrospinal lues.....	60	6	+++	170	++	++	73	2334210000
515	31	Cerebrospinal lues.....	60	14	+++	+++	190	+++	++	31	2233322000
271	36	Cerebrospinal lues.....	30	6	+++	+++	160	++	++	21	3353321000
145	39	Cerebrospinal lues.....	15	5	+++	130	++	++	175	1122100000
101	40	Cerebrospinal lues.....	40	7	+++	+++	200	+++	++	94	2233000000
265	32	Cerebrospinal lues.....	36	6	+++	+++	220	+++	+++	32	2233000000
178	43	Pachymeningitis cervicalis syphilitica	40	11	+++	+++	200	++	++	42	1122331000
351	22	Erb's spastic paraplegia syphilitica	5	5	+++	+++	200	++	++	3	3332220000
747	33	Amiotrophic lateral sclerosis, syphilitic	14	5	+++	+++	170	+++	++	15	0112210000
721	33	Gumma of parietal bone	30	8	+++	150	++	+++	9	0011000000
183	24	Tuberculous meningitis....	55	8	200	+++	+++	90	0000123332

Group III.—Individuals Having Positive Physical Evidence of Organic Nervous Disease but Practically Negative Laboratory Findings

109	33	Tabes dorsalis.....	40	5	170	+	+	4	1122100000
1-12	60	Tabes dorsalis.....	60	7	190	2	1111100000
351	32	Tabes dorsalis.....	22	7	165	+	4	1121000000
7	59	Tabes dorsalis.....	70	10	200	+	+	2
1-5	57	Tabes dorsalis.....	18	7	210	4	0011000000

Group IV.—Individuals Having Syphilis but No Physical or Laboratory Evidence of Central Nervous System Involvement

154	40	Syphilis.....	30	Under 10	+++	130	1	0000000000
120	8	Congenital syphilis.	10	Under 10	+++	160	0	0000000000
4-12	40	Syphilis.....	22	Under 10	+++	160	2	0010000000
2-6	13	Syphilis.....	30	Under 10	+++	130	1	1111000000

Group V.—Individuals Having Physical or Symptomatic Evidence of Central Nervous Disease but Negative Laboratory Findings

100	45	Brain tumor.....	15	10	130	1	0100000000
1-7	50	Jacksonian epilepsy.....	30	9	130	0	0000000000
2-7	40	Jacksonian epilepsy.....	40	6	120	4
4-5	40	Arteriosclerosis.....	51	10	170	0
71	57	Brain tumor.....	40	7	270	1	1111100000
1-2	50	Arteriosclerosis.....	60	7	120	1	0000000000
3-6	57	Arteriosclerosis.....	40	9	150	4	0000000000

—GROUPS OF NORMAL PERSONS AND PERSONS WITH DISEASE OF THE CENTRAL NERVOUS SYSTEM—(Continued)
 Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease.—(Continued)

Urine	Subjective Symptoms	Physical Signs			Bladder	Dysarthria	Ataxia
		Eyes	Knee Jerk	Ankle Jerk			
Normal	Herpes zoster; headache.....	Pupils unequal	Normal	Normal	Normal	None	No
Normal	Pains in legs.....	Pupils fixed	Increased	Increased	Normal	None	No
Few casts	Headaches; excitement	Pupils sluggish	Increased	Increased	Normal	Present	Pres
Few casts	Paresis left hand; headache.....	Optic neuritis	Normal	Normal	Normal	None	No
Normal	Pains in legs; depressed.....	Pupils sluggish	Absent	Sluggish	Normal	None	Sl
Trace alb.	Dizziness; headache; nausea; visual disturbances	Pupils sluggish; optic neuritis	Unequal	Sluggish	Normal	None	Pres
Normal	Pain in neck and arms, with weakness and wasting	Pupils unequal	Normal	Normal	Normal	None	No
Normal	Paralysis of legs.....	Pupils irregular	Exaggerated	Increased	Drizzling	None	Spe
Few casts	Paralysis of legs; pain in legs....	Pupils irregular	Increased	Increased	Normal	Present	Mar
Normal	Stupor; headache	Pupils unequal and dilated	Sluggish	Sluggish	Normal	None	No
Pus cells	Headache; delirium	Pupils unequal	Increased	Increased	Normal	None	No

Group III.—Individuals Having Positive Physical Evidence of Organic Nervous Disease but Practically Negative Laboratory Findings

Normal	Pains in legs; difficult urination...	Pupils sluggish	Absent	Absent	Normal	None	Mar
Normal	Pains in legs; dizziness (Charcot joint)	Pupils sluggish; irregular	Absent	Absent	Drizzling	None	Mar
Normal	Pains in legs; dizziness.....	Pupils irregular	Absent	Absent	Normal	None	Mar
Normal	Pains in legs; headache, dizziness..	Pupils fixed	Absent	Absent	Normal	None	Mar
Normal	Pains in legs; crises.....	Pupils fixed	Absent	Absent	Normal	None	Mar

Group IV.—Individuals Having Syphilis but No Physical or Laboratory Evidence of Central Nervous System Involvement

Normal	Impotence.....	Pupils normal	Normal	Normal	Normal	None	No
Normal	Necrosis of nose.....	Pupils normal	Normal	Normal	Normal	None	No
Normal	Headache and nervousness.....	Pupils normal	Normal	Normal	Normal	None	No
Normal	Headaches; depression; paresthesias	Pupils normal	Increased	Normal	Normal	None	No

Group V.—Individuals Having Physical or Symptomatic Evidence of Central Nervous Disease but Negative Laboratory Findings

Normal	Headache.....	Disks pale	Normal	Normal	Normal	None	No
Normal	Convulsions.....	Normal	Normal	Normal	Normal	None	No
Normal	Convulsions; headache	Normal	Unequal	Unequal	Normal	None	No
Trace alb.	Weakness; headache; blood pressure 240 mm.	Normal	Normal	Normal	Normal	None	No
Normal	Hallucinations.....	Normal	Normal	Normal	Normal	None	No
Few casts	Nervousness; dizziness; paresthesias	Normal	Normal	Normal	Normal	None	No
Few casts	Aphasia; dizziness; weakness; blood pressure 190 mm.	Normal	Normal	Normal	Normal	None	No

The pressures against were increased. The eleven cases of cerebro-spinal syphilis ranged from fifteen to seventy-four minutes, with one exception running twenty-five minutes or over, averaging forty-three minutes. The average age was lower in this group than in the two preceding. The remaining observations ran forty, five, fourteen, thirty and fifty-five minutes, respectively.

It will be observed that all of these persons, with one exception, the patient with Erb's syphilitic spastic paralysis, showed evidence of more or less meningeal inflammation as indicated by pleocytosis, increased globulins, etc. Histologically, also, all of these types of disease are known to exhibit meningeal changes.

In tabes "thickening or cellular infiltration of the spinal meninges, most marked in the posterior portion of the cord," was found present in all of fourteen cases recently studied by Dr. W. F. Schaller,⁵ who is of the opinion that "the tabetic degeneration is a radiculitis subsequent to a primary syphilitic meningitis." This accords with the findings of Spiller,⁶ Bresowsky⁶ and Schröder.⁷ Nageotte believes that the posterior column degeneration is due to an inflammatory process of the radicular nerves involving the perineurium and endoneurium and taking the form of a transverse neuritis, that is just mesial to the spinal ganglia. Here the inflammatory process starts along the posterior columns producing at the same time the characteristic thickenings and round cell infiltration of the meninges throughout the posterior spinal region. This author, with Mott, believes that a considerable absorption of spinal fluid takes place normally by way of the perineural lymphatics which, under the conditions mentioned above, would be greatly impeded.

In paresis Kraepelin⁸ says:

It is not uncommon to find pachymeningitis interna and hematoma of the dura, usually a mere delicate film, but sometimes in the form of a thick coat made up of several layers or of an extensive fresh extravasation of blood, generally on the vertex. One also frequently sees more or less widespread superficial hemorrhages. The pia is always more or less cloudy and thickened, sometimes excessively, especially along the vessels. Microscopic examination shows an increase in the connective tissue and localized infiltrations with lymphocytes and plasma cells. . . . These alterations are generally most apparent over the anterior and middle portions of the hemisphere convexities, also on the inner surface, but less prominent on the basal surface and entirely lacking over the occipital lobes. . . . The veins are greatly distended and

5. Schaller: Early Diagnosis of Tabes Dorsalis, Jour. Am. Med. Assn., 1917, 68, 190.

6. Spiller: Pathology of Tabetic Ocular Palsy, Jour. Nerv. and Men. Dis., 1915, 42, 15.

7. Schröder: Ein Beitrag zur Histopathologie der Tabes Dorsalis. Zentralbl. f. Nerven- u. Psychiat., New Series, 1906, 17, 585.

8. Kraepelin: General Paresis. Nervous and Mental Disease Monographs, No. 4.

often show thickened walls. The Pacchionian granulations are frequently overdeveloped. In the spinal cord one observes occasional pachymeningitis and frequent leptomeningitis more marked over the dorsal columns. . . . Fürstner is inclined to believe that the spinal cord is affected without exception in paresis. The alterations were most severe in the lumbar and dorsal cord and gradually diminished as they were followed upward. Alzheimer and others have demonstrated infiltration of the vessels with lymphocytes and plasma cells, both in the pia and in the cord itself.

Barker⁹ says: "The pathologic basis of cerebrospinal syphilis consists of a syphilitic infiltration and gumma formation that affects the vascular system and the meninges and the white and gray matter of the brain and cord." Spiller thinks that in all these forms of syphilitic disease the process is not limited, but is an involvement of the whole cerebrospinal tract, being only more pronounced in certain areas in the different clinical types.

The widespread vascular and meningeal involvement in these three clinical forms of disease may account for the small degree of difference in their average appearance time. As before noted, these averages were forty-two, thirty-six, and forty-three minutes, respectively. The widest range was in cerebrospinal syphilis, fifteen to seventy-four minutes.

Pachymeningitis cervicalis hypertrophica syphilitica is by definition a meningeal disease. Whether the delay in this instance was due to changes in the absorbing power of the meninges of the cord, or whether it was due to blocking of the circulation to cerebral absorbing areas, is not certain.

As indicated in the table the case of amyotrophic lateral sclerosis showed definite evidence of syphilis of the central nervous system with meningeal involvement. Spiller¹⁰ cites two cases which were "typical clinically and pathologically of amyotrophic lateral sclerosis," and which showed round cell infiltration in the pia typical of syphilitic disease in addition to the usual systemic degeneration. This meningeal infiltration, though probably not extensive, would perhaps account for the very slight delay in the phenolsulphonephthalein excretion. On the other hand, the patient with Erb's paraplegia, with no signs of meningeal inflammation in the fluid, gave a normal excretion time.

The patient with gumma of the parietal bone, while listed separately, might have been included among those with cerebrospinal syphilis, having evidence of meningeal inflammation in the pleocytosis and increased globulin and albumin.

The case of tuberculous meningitis, the only nonsyphilitic disease in this group, came to necropsy and showed very extensive thickening and edema of the meninges of both the brain and cord.

9. Barker: *Monographic Medicine*, 1916, 4, 549.

10. Spiller: *Syphilis as a Cause of Systemic Degeneration of the Motor Tract*. *Jour. Nerv. and Ment. Dis.*, 1912, 39, 584.

Group III.—This group consists of five clinical tabetics who differ from the foregoing only in the meager pathologic findings in the spinal fluid, all having negative Wassermann, Nonne and Noguchi reactions, cell counts (four or less), and practically negative colloidal gold reactions. Three of these were negative when first observed; two had been thoroughly treated and were negative at the time of these observations. It will be noted, however, that the average excretion time was forty minutes, only two minutes less than that of the tabetics in the foregoing group. This suggests one possibility of a diagnostic significance for this method.

Group IV.—This group represents four syphilitics with no laboratory or physical evidence of central nervous system disease. Their average was twenty-one minutes, or somewhat more than twice that found in the normal controls. The value of this procedure in detecting early involvement of the central nervous system will be further considered in a subsequent communication.

Group V.—This is a mixed series of seven persons having definite physical or symptomatic evidence of organic disease of the central nervous system, but with negative spinal fluids. None of these were syphilitics. The average appearance time was forty-five minutes. There was no definite correspondence to age, nor were the spinal fluid pressures definitely increased. The group represents one brain tumor, two cases of jacksonian epilepsy, three of advanced arteriosclerosis and one of delirium tremens. It is conceivable that in these individuals more or less extensive involvement of the vascular or lymphatic apparatus might exist. This, though not actively inflammatory giving rise to pleocytosis and increase in globulins, might account for the delayed excretion.

In attempting to explain these delays in more than a general way one is met by several difficulties. If one presupposes a limited area of absorbing tissue, the cerebral arachnoid villi for example, a uniform damage to this area would have to be assumed, or that some obstruction to the free flow of the phenolsulphonephthalein to this area must exist. In some such way the wide range of results in persons having the same type of disease, cerebrospinal syphilis, for example, might be explained. Until more necropsies are secured no more definite information as to the method of excretion of the phenolsulphonephthalein can be given by this procedure. It would seem, however, that inflammations involving the meninges with consequent vascular and lymphatic changes cause a delayed excretion of the dye. Even in those instances in which the symptomatology would suggest a localized lesion, the delay in the appearance time would raise the question of a generalized involvement of the meninges.

SUMMARY

1. Phenolsulphonephthalein when injected into the subarachnoid space in normal persons appears in the urine in ten minutes or less.
2. Diseases of the central nervous system, especially when involving the meninges, produce a lengthening of the appearance time to as much as seventy minutes in some cases.
3. This delay cannot be accounted for by disease of the kidneys, or by the reduction of the phenolsulphonephthalein in the spinal fluid.
4. Advanced general arteriosclerosis may be a factor in causing the delay in some instances.
5. In syphilis a lengthening of the appearance time may be produced before any other evidence of central nervous system involvement has appeared.
6. The method may prove of value in detecting instances of organic central nervous system disease in which the ordinary spinal fluid findings are negative or incomplete.
7. At this time no definite conclusion can be drawn as to the exact location of the absorbing tissues.

It is a pleasure to acknowledge our indebtedness to Drs. W. F. Schaller, A. W. Hewlett and A. W. Hoisholt for material and for valuable suggestions. Also to Miss Beatrice Howett and Mr. R. W. Wilcox for technical assistance.

A STUDY OF THE ERYTHROCYTES IN A CASE OF SEVERE ANEMIA WITH ELONGATED AND SICKLE-SHAPED RED BLOOD CORPUSCLES *

VICTOR E. EMMEL, PH.D.

CHICAGO

I. INTRODUCTION

The present data relates to the blood corpuscles of a mulatto woman who entered the Washington University Hospital, St. Louis, Nov. 3, 1914. The unusual character of the blood picture at once attracted attention and became the subject of extended study by several members of the hospital staff. The clinical data need not be elaborated, as the history of the case up to June, 1915, has been fully recorded by Drs. J. E. Cook and J. Meyer.¹

The patient, aged 21, entered the hospital with an ulcer on the leg. The ulcer healed under treatment and after her discharge from the hospital, Dec. 3, 1914, the patient gained in weight and showed general improvement. An ulcer had appeared on the leg at two previous times in her history, the first at the age of 5, and the second at the age of 19. In both instances, with treatment, it soon healed. The third appearance occurred ten month previous to the patient's entering the hospital. Aside from this ulceration the physical examination otherwise furnished apparently little data of evident significance. Examinations for syphilis or parasites were negative. The blood picture constituted the most striking feature of the case and has been more or less persistent up to date, a period of over two and one-half years.

The unusual structural characteristics of the blood corpuscles, together with two apparently similar cases described by J. B. Herrick,² and R. E. Washburn³ seems, as stated by Drs. Cook and Meyer, to justify the conclusion that "we have in these three cases a group which belongs quite apart from anything heretofore described."

My own observations were begun with the purpose of making a detailed study of the peculiar types of red blood corpuscles occurring in this blood and to ascertain if possible their mode of origin and the

* Submitted for publication May 17, 1917.

* From the Department of Anatomy, University of Illinois College of Medicine.

1. Cook, J. E., and Meyer, J.: Severe Anemia with Remarkable Elongated and Sickle-Shaped Red Blood Cells and Chronic Leg Ulcer, *THE ARCHIVES INT. MED.*, 1915, **16**, 644.

2. Herrick, J. B.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, *THE ARCHIVES INT. MED.*, 1910, **6**, 517.

3. Washburn, R. E.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, *Virginia Med. Semi-Month.*, 1911, **15**, 490.

factors involved. The blood was studied in fresh hanging drops, stained preparations and under experimental conditions. The observations on the patient were continued at various intervals during the year following her discharge from the hospital, that is, up to Jan. 1, 1916. Certain aspects of the experimental study as originally planned remain incomplete, but as the work was unavoidably interrupted at the latter date, it has appeared desirable to record at the present time the results so far attained. The work was begun at the Washington University Medical School and completed at the University of Illinois. College of Medicine. The author is indebted to Dr. George Dock of the Department of Internal Medicine of the Washington University Medical School for the opportunities placed at his disposal, and to Dr. C. S. Williamson of the University of Illinois for access to ward patients at the Cook County Hospital. I wish also to express my appreciation of the material assistance, including the use of loan preparations from Herrick's and Washburn's cases, received through the kindness of Drs. Cook and Meyer.

II. GENERAL CYTOLOGIC CHARACTERISTICS OF THE ERYTHROCYTES

The present account relates to conditions in the blood as observed from December, 1914, to June, 1915. Certain changes which occurred in the latter part of the year 1915 will be subsequently noted. Figure 1, made from a stained blood preparation taken in December, 1914, illustrates some of the general structural characteristics of the red blood corpuscles. Instead of presenting the typical rounded disk form, about one-third of the corpuscles are greatly elongated in shape. A large percentage of the latter have a rounded, rod-like shape with more or less tapering ends, and as a rule present a curved or crescentic form (Fig. 1). These crescentic or sickle-shaped elements as observed in stained preparations are homogeneous in structure, and as a rule take, if anything, a darker hemoglobin stain than the disk-shaped corpuscles.

In addition to this remarkable deviation in form the erythrocytes also differ considerably in size. The smaller cells generally take a deeper hemoglobin stain, the lighter or more transparent central area typical of the biconcave disk is usually lacking and the corpuscle is apparently homogeneous in structure and density throughout. Some of the erythrocytes are paler than others and are apparently correctly described as polychromatophilic. Certain other structural variations will be subsequently described. "The red cells varied in number between 1,800,000 and 3,100,000, usually about 2,500,000" (Cook and Meyer,¹ pp. 647-650). It was also determined by Dr. Cook that in blood collected in an isotonic solution to which sodium citrate had been added, and treated against a hypotonic solution, the resistance of the

red cells did not differ materially from normal conditions. Hemolysis was slight at 0.53, marked at 0.29 and complete at 0.25. Nucleated red cells occurred in all preparations. In most cases the nuclei presented the small compact or pyknotic condition of the more highly differentiated normoblast. In some of the smaller sized and less differentiated nucleated corpuscles the nuclei were larger and had the open chromatin network of the younger erythroblast. It is of interest to note that not infrequently there is to be observed a rim of cytoplasm immediately surrounding the nucleus which takes a deeper cytoplasmic stain than the more peripheral part of the cytoplasm, as suggestive of structural differences between the nuclear and cytoplasmic poles of the differentiated erythroblast, in a manner comparable to conditions apparently occurring in the erythroblasts of the embryonic circulation.⁴ Erythroblasts were also observed in which the cytoplasmic pole presented the appearance of having already assumed a biconcave disk shape previous to the formation of the nonnucleated red corpuscle or erythroplastid (Fig. 3). Interest attaches to this fact as furnishing further evidence that the assumption of the disk or cup form of the erythrocyte is not necessarily dependent on the extrusion of the nucleus, as has been maintained by several investigators (Emmel⁴ pp. 136, 143). It is perhaps to be taken into account that the assumption of this disk shape may possibly be more precocious in this blood than is normally the case for the adult.

Punctate basophilia is not of infrequent occurrence in the nucleated red cells. This cytoplasmic condition was, however, never observed in either the disk-shaped or sickle-shaped nonnucleated erythrocytes. Sickle-shaped corpuscles containing nuclei were not observed. Jolly bodies or Cabot rings were not found. It is of interest to note that there was evidence of phagocytic ingestion of erythrocytes in the peripheral circulation. The cells in which these erythrocytic inclusions were found were apparently of the large lymphocytic or mononuclear type. Certain observations concerning the blood platelets will be described in a separate article.⁵

III. ORIGIN OF THE SICKLE-SHAPED ERYTHROCYTIC ELEMENTS

One of the first questions to present itself concerning these remarkable sickle-shaped erythrocytes relates to their source of origin and mode of formation. In the adult organism the chief source of the non-

4. Emmel, V. E.: Concerning Certain Cytologic Characteristics of the Erythroblasts in the Pig Embryo and the Origin of Nonnucleated Erythrocytes by a Process of Cytoplasmic Constriction, *Am. Jour. Anat.*, 1914, **16**, 127, 141, 147, 148.

5. Emmel, V. E.: Observations Regarding the Erythrocytic Origin of Blood Platelets, in press, *Jour. Med. Research*, 1917.

nucleated red corpuscles is found in the red bone marrow. Do these elongated forms arise in situ in the same blood-forming organ as an abnormal or end-phase in the cytomorphosis of the erythroblast, or may the nonnucleated element develop as a typical biconcave disk or cup-shaped corpuscle in the bone marrow and undergo further transformation after their passage into the general systemic circulation? Furthermore, in either case how does this transformation take place? With reference to these questions the following data have been derived from stained and fresh blood preparations. In the first instance it may be observed that the fact that none of the sickle-shaped forms were found to contain nuclei, in itself indicates that the assumption of the sickle-shaped form primarily takes place subsequent to the formation of the nonnucleated erythrocyte or erythroplastid from the erythroblast. If this occurs in the circulating blood one would expect to find various stages of the process in the peripheral circulation.

As already indicated, about two-thirds of the circulating red blood corpuscles present a more or less typical biconcave disk shape. At the other extreme are the striking sickle-shaped forms. On closer study, however, it became evident that stages apparently transitional in character could be found between these two types. This is illustrated in Figure 2, in which *a* represents a typical biconcave disk-shaped red corpuscles; *c* and *f* corpuscles possessing two blunt processes situated at opposite margins of the disk; *g* and *h* present the appearance of half disks and *i-k* are intermediate in form between *g* or *h* and the sickle-shaped elements *l-o*. These various forms strongly indicate that the transformation of the red disks into the sickle-shaped elements is taking place in the circulating blood—a conclusion which appears definitely substantiated by the behavior of the erythrocytes in culture preparations.

In a further study of these stages certain interesting structural characteristics are to be observed. In the first place, while there is a gradual increase in the length of the long axis from corpuscles *l-o* in Figure 2, the actual length of the circumference of the arc of the sickle-shaped elements instead of being longer is approximately equal, or, if anything, less than that of the normal disk-shaped erythrocytes. Second, certain structural differences are to be noted between the sickle-shaped elements and the intermediate forms. While the former have a more or less evenly rounded or rod-like contour, corpuscles like *g* still present a flattened disk-like shape. This can be clearly demonstrated by manipulation of the fresh blood under a cover glass in such a way as to rotate the corpuscle while under observation. This is illustrated in Figures 13 and 16, representing camera lucida drawings of two views of the same corpuscle. In each case *a* represents a side view and *b* a profile view of the same corpuscle. Again in *g*, *h*

and *i* and the same is true for Figures 14 and 15, a convex periphery of the more or less crescentic elements takes a deeper hemoglobin stain and presents the form of a thickened rib-like border. In contrast to this the opposite or concave margin of the corpuscle is very thin and relatively more transparent. In *j* and *k* this thin margin has practically disappeared, but there still remains a decided bulging at the center of the crescent, giving it something of a spindle-shaped form. Finally, there is to be noted a form which is evidently correctly interpreted as intermediate between the normal erythrocytic disk and the crescentic forms. This is illustrated in *b*, *c* and *d* in Figure 2, and also in Figures 8 and 9, in which the concavity of the corpuscle instead of being centrally placed is eccentric in position. Consequently the erythrocyte presents a thin flattened region at one side while the remainder of the corpuscle assumes a thickened crescentic form.

These structural characteristics are suggestive as to the manner in which the original disk-shaped erythrocytes may be transformed into the sickle-shaped elements. There is a substantial and growing body of facts indicating that the mature erythrocyte is surrounded by a membrane consisting in part at least of such lipoid substances as lecithin and cholesterin and that the surface tension associated with the membrane of this composition is of such a character as to be an important factor in the production of the flattened biconcave form of the erythrocyte. (Compare also Emmel,⁴ pp. 144, 145.) In the normal erythrocyte this depression or concavity is centrally situated and the periphery of the disk has the form of a thickened ring. In the present blood the erythrocytes have evidently undergone structural changes of such a nature that the concavity of the corpuscle may become displaced toward one side of the erythrocyte. Accordingly, the contents of the erythrocytic disk becomes rearranged in the form of a thickened broad crescent, the extremities of which are united by the much thinner membranous part of the corpuscle. The various stages shown in Figures 2, 8, 9 and 10 suggest that this thinner margin gradually retracts, the thickened crescent becomes more rounded and rod-like, and with the wider separation of its ends assumes the sickle-shaped form found in the circulating blood. What appear to be identical transition stages between disk-shaped and sickle-shaped erythrocytes were also present in the blood preparations from Herrick's (Figs. 8-10) and Washburn's cases.

IV. BEHAVIOR OF THE ERYTHROCYTES UNDER EXPERIMENTAL CONDITIONS

(*a*). *Cultures from the Patient's Blood.*—If the preceding conclusion is correct, that the transformation of the erythrocyte into the sickle-shaped form is taking place in the circulating blood rather than

being necessarily confined to the blood-forming organs, it becomes of interest to ascertain the changes which may occur in cultures of the fresh blood. For this purpose culture preparations were made under sterile conditions. A ring of petrolatum was drawn on a carefully cleaned glass slide. A clean sterile cover glass was then brought in contact with a drop of fresh blood and the cover glass quickly placed on the slide in such a way as to bring the drop of blood to the center of the vaselin ring. The edges of the cover glass were also sealed with sterile petrolatum, so as to form an air-tight chamber similar to that used for tissue culture purposes. These preparations were kept at room temperature and observed at two- or three-hour intervals. Within a few hours such preparations show a marked increase in the elongated type of cells. Great numbers and in some cases the majority of the previously apparently normal disk-shaped erythrocytes become transformed into elliptical spindle-shaped and sickle-shaped elements. A prominent feature in the cultures as compared with the freshly drawn blood is the extension of the tips of the spindle-shaped and crescent-shaped forms into long, tapering, hair-like processes (Figs. 11 and 14). The great abundance of these structures make a striking picture when viewed microscopically. It was thought at first that these needle or hair-like processes were merely fibrous threads arising through clotting; but the cells were found to be freely movable in the plasma and were not attached or held in any fixed position by a fibrous network. By careful manipulation of the cover glass by means of pressure with a needle point, the corpuscles could be turned over and viewed from all sides. During such manipulation each corpuscle maintained a fixed form. Although the erythrocytes in this blood can be observed to be abnormally soft and pliable, no success was obtained in bringing about a mechanical transformation of a disk-shaped corpuscle into a sickle-shaped form.

In a further study of the conditions under which these changes occurred in the cultures the following points may be noted. Alterations in form as the result of overheating is eliminated, since the preparations were kept at room temperature. The processes in question can be clearly recognized as in direct continuity with the cytoplasm of the red corpuscle, and in the majority of cases are evidently not to be confused with fibrin formations. Some of the preparations were kept for eight or more days without any further evident changes in the structure or contour of the sickle-shaped elements. It was suggested that the petrolatum used in sealing the preparations by coming into contact with the blood might be a factor in the result, but it was found that the same transformations could be obtained in paraffin-sealed cultures. It may be noted that the elongation of the erythrocyte and the formation of the attenuated processes was not as marked in a free

hanging drop as in the preparations in which the culture drop was in contact with the two adjacent surfaces of the cover glass and slide, but no adequate explanation for this difference was suggested. Since the hanging drop is of course not in contact with the petrolatum sealing the preparation, some attention was given to this point, but as already indicated, the petrolatum is not a factor in the transformations. The matter was also further tested by bringing a small cover glass (about 12 mm. in diameter) into contact with the underside of the culture drop where it would be held in position by capillary attraction. One edge of this disk had also been slightly thickened or bent by heating in order to prevent a compression of the enclosed blood corpuscles. In such preparations the erythrocytic changes were abundant. No conclusive data were obtained from a few preparations kept in both moist and dry chambers. The possibility was also considered as to whether the phenomenon could be placed in the category of crenation processes. This was suggested by the fact that in some cases erythrocytes were observed which had assumed many-pointed, star-shaped forms (compare Fig. 24) representing, probably, abnormal cases of crenation, due no doubt, to the changed structure of the erythrocyte. This possibility, however, appears eliminated through the fact that the erythrocytes undergo the same sickle-shaped changes in preparations in which there was but little, if any, evidence of crenation to be found. Occasionally the sickle-shaped corpuscles themselves manifest the small surface projections typical of crenation.

Most of the above observations were made on blood obtained in January, 1915. At that time and during the next few months the blood picture was comparable to Figure 1. As already indicated, the patient had been discharged from the hospital early in December, 1914, showing general physical improvement. During the latter part of the summer of 1915, however, in consequence of a reappearance of the leg ulcer and a general weakened condition, the patient returned to the hospital. On making an examination of the blood in the ensuing September, I was surprised to find an almost entire absence of the sickle-shaped erythrocytes (Fig. 17). It was only after careful examination that an occasional elongated erythrocyte could be found in a stained preparation. Otherwise the red corpuscles presented a practically normal picture, and in a casual observation could readily be classified as representing normal conditions, at least so far as the erythrocytes were concerned. The contrast is strikingly shown in a comparison of Figures 16 and 1. This result was verified by repeated observations on blood taken at different times. During the next three months (that is, up to Jan. 1, 1916, when the present observations were terminated) the red blood corpuscles continued to present practically the same appearance. Aside from the fact that during this period a positive

Wassermann reaction was obtained (whereas earlier tests had been negative) nothing conclusive was ascertained which would account for this disappearance of the sickle-shaped forms from the circulation. On subsequent inquiry I learned that the sickle-shaped erythrocytes gradually reappeared in the patient's blood.⁶

The interesting question naturally at once arose as to the behavior of the red cells under experimental conditions as compared with the results obtained in January, 1915. For this purpose sterile petrolatum sealed cultures were made as in the former case and kept at room temperature. The result was indeed striking. Within one hour a large number of the erythrocytes had assumed beautiful crescentic and sickle-shaped forms (Figs. 18 and 19). Within six hours the sickle-shaped forms were present in great abundance, and in twenty-four hours in some of the preparations almost all of the erythrocytes had undergone a similar transformation. There was very little if any evidence of crenation. The experiment was repeated several times, but always with the same result. Some of the preparations were kept for eight days or longer, and great numbers of these elongated and sickle-shaped erythrocytic elements were persistent throughout this time. The evidence appears conclusive that even though for some unknown reason the circulatory erythrocytes had temporarily returned to an apparently more normal structure, they still retained the potentiality for transformation into the sickle-shaped forms.

(b) *Comparison with Erythrocytes from Normal Blood and from Cases of Anemia, Chlorosis and Leukemia.*—In considering the preceding results, the question arises, is this behavior of the erythrocytes specific for this case or type of blood disease, or may the same reaction be obtained from other blood? In the endeavor to answer this question, culture cases of anemia and chlorosis were obtained at the Barnes Hospital, St. Louis, and also cases of pernicious anemia and myelogenous leukemia at the Cook County Hospital, Chicago. The preparations were made in identically the same manner as in the previous experiments and kept at room temperature. In the case of the normal blood, in some instances the blood drop was placed under the same coverglass with a drop of blood containing the sickle-shaped corpuscles, the two specimens of course not being allowed to come in contact with each other. Figures 11 and 12 are drawings from such a preparation kept at room temperature for five days. The erythrocytes in the nor-

6. For this information I am indebted to Dr. Cook for a personal letter in April, 1916, in which he also expresses the opinion that the positive Wassermann had nothing to do with the blood picture, and says that "in all probability she acquired her lues recently, for she returned to her husband between the time of her first and second stay in the hospital, and she knew that he suffered from venereal disease. There is, moreover, no reason to distrust the first Wassermann reactions."

mal blood (Fig. 12), aside from a slight crenation in some of the corpuscles, manifested no further changes as compared with the elongated sickle-shaped forms (Fig. 11). In the cultures made from the cases of anemia, chlorosis, and myelogenous leukemia the erythrocytes in no instance presented form changes comparable to that of the sickle-shaped erythrocytes.

On the basis of the present experiments, therefore, it appears that the erythrocytic changes observed in the culture preparations are specific for the case of anemia with sickle-shaped corpuscles. It will be of great interest to ascertain to what extent this conclusion will prove true in further experiments on both pathologic blood and other cases of sickle-shaped corpuscles which may be subsequently discovered.

(c) *Cultures from the Blood of the Patient's Father.*—In connection with the present subject there is to be described an interesting exception to the foregoing results. This occurred in the case of cultures made from blood of the patient's father. Fresh and stained blood from the father appeared quite normal (Fig. 20). The erythrocytes uniformly presented the typical biconcave disk-shaped form. In January, 1915, culture preparations were made and kept at room temperature. When examined at the end of twenty-four hours, some of the erythrocytes were found to have assumed elongated and sickle-shaped forms (Figs. 21, 22 and 23). The tips of some of the crescents were drawn out into slender tapering processes (Fig. 22). These elongated forms were by no means as abundant as in the patient's blood, but otherwise they appeared entirely comparable to the forms found in her blood. When the next opportunity occurred to see the father again, nearly a year later, his blood still presented an apparently normal condition, but in the culture preparations the erythrocytes again manifested the same tendency toward a transformation into elongated and sickle-shaped forms.

On obtaining this experimental result with the father's blood, a further study was made of stained preparations to ascertain whether any other hematologic features common to both father and daughter could be discovered. The father, a mulatto, aged 54, was apparently in normal health. An analysis of his blood gave 4,500,000 red cells, 11,100 white cells and 86 per cent. hemoglobin (compare Cook and Meyer, Footnote 1, p. 648). The absence of elongated or sickle-shaped red cells in the father's blood has already been indicated. On the other hand, there is to be noted a frequent occurrence of nuclear excrescences in the neutrophils in both cases, as illustrated in Figures 4, 5 and 6. The apparent association of such leukocytic forms with

certain diseases, Gruner,⁷ is suggestive of abnormal conditions in the father's blood. Similar excrescences were not observed in the eosinophils. Some of the mononuclear cells in the father's blood contained phagocytic inclusions, but that they were erythrocytic in nature could not be established with certainty. In general, it may be noted that the father's blood is in many respects comparable to the condition of the patient's blood in December, 1915, at which time the sickle-shaped form had practically disappeared from the circulation. With reference to other members of the same family, it may be stated that there were three other children all of whom died at an early age. The mother died of breast cancer. It is of interest to note that all the children suffered from severe anemia (compare also Cook and Meyer¹).

(d) *Effect of Patient's Serum on Erythrocytes from Other Individuals.*—The conclusion that a transformation of normal erythrocytes to sickle-shaped forms is taking place in the peripheral circulation directs attention to chemical or other characteristics of the blood plasma as possible factors productive of these cytologic changes. While this phase of the study remains incomplete, certain results may, however, be recorded with reference to the effect of the patient's serum on erythrocytes taken from the blood of other individuals. With this in view, blood was removed from the patient under aseptic conditions, allowed to clot, centrifuged, and the supernatant serum removed for experimental purposes. Using this serum as a medium, two series of cultures were made comparable to the preparations described in the preceding experiments. To one of these series, normal blood from a healthy individual had been added, and to the other blood taken from a case of pernicious anemia. Observations were made at various times during the next three or four days with the following results. In the case of the normal blood the erythrocytes became softer and more pliable and showed a tendency to adhere to each other. In the case of the anemic blood, however, the erythrocytes were not only adherent in cords and masses, but quite a number of them eventually presented more or less elongated and crescentic forms with pointed tapering processes comparable to those observed in the patient's blood. In a second experiment cultures were made in which the patient's erythrocytes were placed in serum derived from normal blood. Crescentic forms with tapering, hair-like processes developed just as in the cultures from the patient's blood, but were much less numerous (Fig. 16). Evidently transformation of the patient's erythrocytes will continue to a limited extent even in normal serum. A possible criticism which here suggests itself is that in the case of the first experiment the cen-

7. Gruner, O. C.: A Study of the Changes Met With in the Leukocytes in Certain Cases of Malignant Disease, *British Jour. Surg.*, 1915, **3**, 506.

trifuged serum might still have retained a few of the patient's corpuscles and thus account for the forms found in the cultures of anemic blood. While no microscopic examination of the serum was made, there is no reason to suspect that it contained erythrocytic elements from the patient. In the first place, crescentic forms were not observed in the cultures when first made, and second, if such erythrocytic elements were present it would have been expected that crescentic forms would have appeared in the cultures made from normal blood.

In conclusion, it is perhaps not irrelevant to direct attention to certain general aspects of the present phenomenon. The investigations of the pathologist not infrequently bring home the fact that what are designated as abnormal or pathologic processes are frequently, after all, in their fundamental character primarily either inhibitions or accentuations of normal properties of tissue cells. The erythrocyte, in contrast to the majority of static, nonameboid tissue cells, is an isolated, free-floating element, the form of which is determined, not by its mechanical relations to adjacent tissue structures, but by an interaction with the chemical elements of a fluid, the blood plasma. In this medium the erythrocyte, as is well known, tends to assume a flattened form, an obvious advantage of which consists in the presentation of a greater surface for oxidation. This tendency in the differentiation of the erythrocyte finds its most striking expression in the biconcave disk-shaped corpuscle of mammals (compare also Emmel,⁴ p. 136).

With reference to our present subject, the suggestion arises that the transformation into crescentic or sickle-shaped forms may be due, in part, at least, to the abnormal or accentuated activity of the same factors which, in the normal hematogenesis of vertebrates, have led to the transformation of the original spherical red blood corpuscle into the biconcave disk-shaped erythrocyte of the adult mammal. In the case of the present patient, the reaction between the erythrocyte and the presumably altered blood plasma is such that the incidence of the factors producing the concavity of the corpuscle is no longer rigidly confined to the center of the disk, with the result that the thinned portion of the corpuscle may shift to one side and the hemoglobin content accumulate in a crescentic configuration at the opposite side of the erythrocytic disk. In consequence of the abnormally softened character of the erythrocytic membrane in anemic blood, the attenuated peripheral margin of such a disk gives way or retracts from the horns of the crescent and there remains the crescentic or sickle-shaped erythrocytic element.

While the present sickle-shaped forms occurred under pathologic conditions, it is interesting to note that apparently similar forms have

been described by Gulliver⁸ in the blood of the Mexican deer and Persian deer, where the blood, aside from the usual disks, contained quite a number of less regular forms, some of which he describes as "curved and gibbous in the middle, and acutely pointed at the ends, with a concave and convex margin, like a crescent."

V. SUMMARY

1. General erythrocytic characteristics.

(a). About one third of the erythrocytes instead of presenting the normal disk-form are greatly elongated in shape. A large percentage of the latter have a crescentic or sickle-shaped form.

(b). Nucleated erythrocytes occurred in all preparations. Some of the normoblasts present a biconcave disk-shape. Punctate basophilia occurs in many of the nucleated red corpuscles, but was not observed in either the disk-shaped or sickle-shaped nonnucleated corpuscles. Jolly bodies or Cabot rings were not found.

(c). Phagocytosis of erythrocytes is taking place to a certain extent in the peripheral circulation.

2. Origin of the sickle-shaped forms.

Evidence was advanced indicating that the circulatory erythrocytes undergo structural changes of such a nature that the central concavity of the normal disk becomes displaced to one side and the hemoglobin content accumulates in a crescentic form at the opposite side of the erythrocytic disk. That the thin margin of this disk retracts, the crescentic part becomes more rod-like and with the wider separation of its ends assumes the sickle-shaped forms under consideration, instead of the poikilocytes usually encountered in anemic blood.

3. Behavior of the erythrocytes under experimental conditions.

(a). In culture preparations kept at room temperature it was found that great numbers of the previously disk-shaped corpuscles became transformed into elongated and crescentic elements. The tips of the latter were frequently extended into tapering hair-like processes.

(b). During one period of the study, for some unknown reason, the abnormal crescentic forms had temporarily disappeared from the circulation. In culture preparations, however, the erythrocytes still manifested the tendency to assume elongated and crescentic forms.

(c). Similar cultures from normal blood and from cases of pernicious anemia, chlorosis and myelogenous leukemia gave only negative results.

8. Gulliver: Proc. Royal Soc. London, 1842, p. 199.

(*d*) An interesting exception was obtained in the case of the patient's father. In this instance the circulatory erythrocytes presented an apparently normal structure, but under culture conditions occasional corpuscles were found to assume elongated and crescentic forms.

(*e*). In culture preparations made by placing erythrocytes from a case of pernicious anemia in the centrifuged serum of the patient's blood, some of the red corpuscles assumed characteristics comparable to those observed in cultures of the patient's blood.

4. In conclusion, it may be stated: (*a*) that the culture reaction of the erythrocytes appears to be specific for this case of anemia, and (*b*) that the manner in which the red blood corpuscles are transformed into the sickle-shaped elements suggests that the phenomenon is in part at least due to an accentuated or abnormal activity of the same factors which in normal hematogenesis are involved in the transformation of the original spherical erythrocyte into a biconcave disk-shaped form.

PLATE I

Fig. 1.—From a stained preparation of the patient's blood made in December, 1914.

Fig. 2.—Drawings from the same preparations as in Figure 1, to illustrate the various types of erythrocytic elements apparently intermediate between the normal biconcave disks (*a*) and the sickle-shaped forms (*o*).

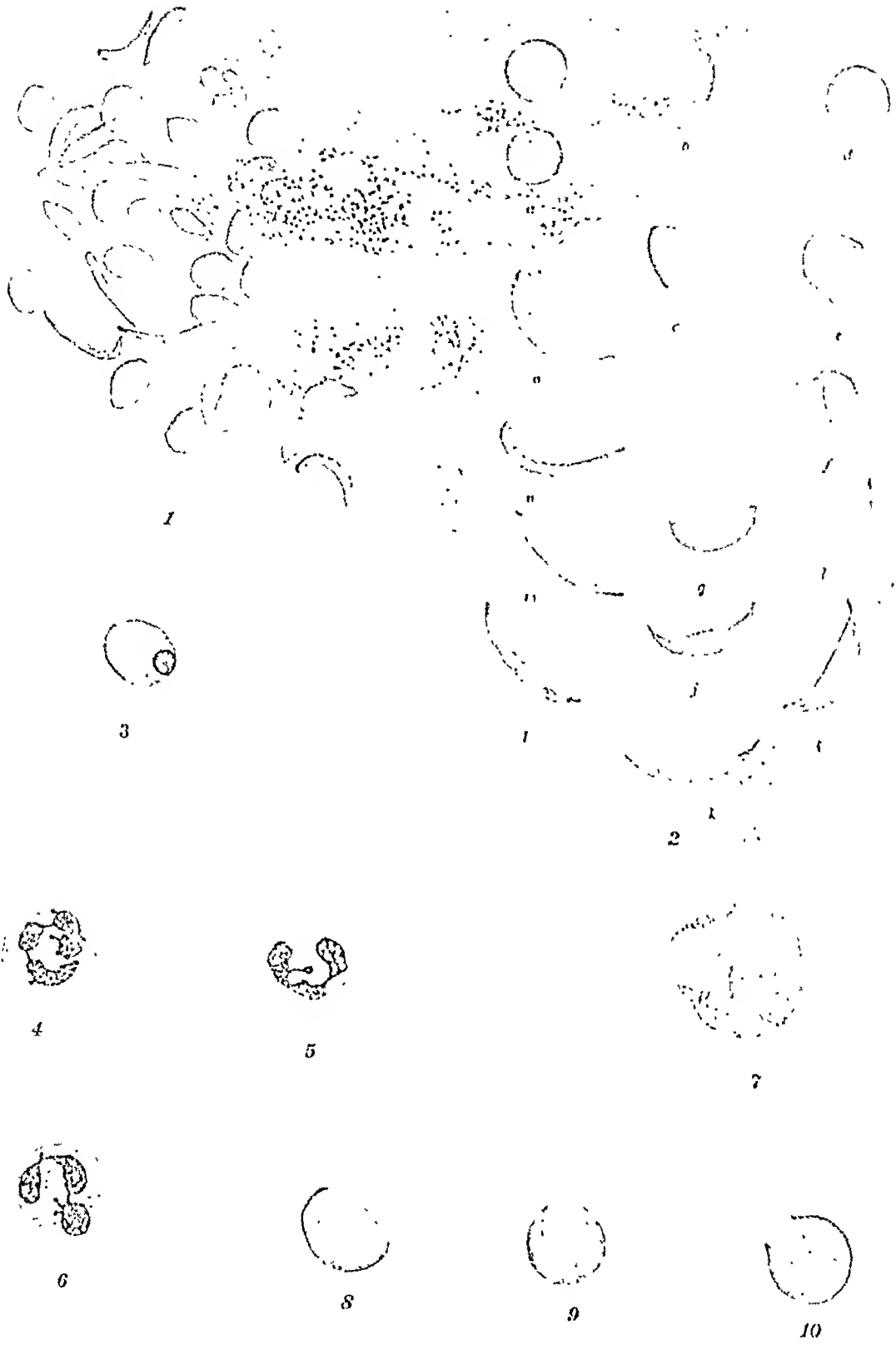
Fig. 3.—A nucleated erythrocyte in which the hemoglobin containing cytoplasm has assumed a biconcave or possibly cup-shaped form previous to its differentiation into a nonnucleated element. From the same source as Figures 1 and 2.

Figs. 4, 5, and 6.—Neutrophils showing nuclear excrescences. Figures 4 and 5 from the patient's blood in January and December, 1915, respectively. Figure 6 from the patient's father, December, 1915.

Fig. 7.—Phagocytosis of erythrocytes (2) in the peripheral circulation.

Figs. 8, 9 and 10.—Erythrocytes from Herrick's case of severe anemia with sickle-shaped red blood corpuscles.

PLATE I



REMARKS ON THE CHOLESTEROL CONTENT OF HUMAN BLOOD*

FRANK D. GORHAM, M.D., AND VICTOR C. MYERS, Ph.D.
ST. LOUIS NEW YORK

Judging from the extensive literature which has accumulated on cholesterol during the past ten years, this lipoid has been the subject of more varied and extended investigations than any other substance of physiologic importance. Although it has received the attention of organic and physiologic chemists and clinical investigators alike, its exact constitution and much concerning its rôle in normal and abnormal metabolism remains to be solved. It is known, however, that cholesterol is a monatomic, simple, unsaturated, secondary alcohol. It further possesses the character of a complicated terpene, which gives it a unique position in the animal organism, since no other substance has been found to have so complicated a carbon nucleus except cholic acid, which alone is analogous.

The importance of cholesterol is indicated by its widespread occurrence in the animal body. Cholesterol is obviously, therefore, a constituent of our various animal foods, from which probably much of the cholesterol of the body is derived. According to Fraser and Gardner,¹ the phytosterols of the plant foods are transformed to cholesterol in the body, evidently furnishing a portion of our supply of this substance. Whether or not cholesterol is synthesized in the body, remains a disputed question. Lifschütz² believes that it may be formed from oleic acid, and also that it holds some genetic relationship to cholic acid,³ since the same color reactions may be obtained after oxidation with benzoyl peroxid. In testing out the possibility of a transformation of cholesterol to cholic acid, Goodman⁴ found that cholesterol, injected directly into the circulation, appeared to have but slight influence on the elimination of cholic acid. Rosenbloom and Gies⁵ have also discussed the possible derivation of cholic acid and

* Submitted for publication April 30, 1917.

* From the Laboratory of Pathologic Chemistry, and Department of Internal Medicine, New York Post Graduate Medical School and Hospital.

1. Fraser, M. T., and Gardner, J. A.: *Proc. Roy. Soc., London (B)*, 1910, **82**, 559; Ellis, G. W., and Gardner, J. A.: *ibid.*, 1912, **85**, 385.

2. Lifschütz, J.: *Ztschr. f. physiol. Chem.*, 1908, **55**, 1.

3. Lifschütz, J.: *Ztschr. f. physiol. Chem.*, 1914, **92**, 383.

4. Goodman, E. H.: *Beitr. z. chem. Physiol. u. Path. (Hofmeister's)*, 1907, **9**, 91.

5. Rosenbloom, J., and Gies, W. J.: *Biochem. Bull.*, 1911-1912, **1**, 51.

bile salts (cholates) from cholesterol. They suggest that gallstones may arise when, among other causes, the transformation of cholesterol into bile salts is materially diminished, with a consequent marked increase in the concentration of cholesterol in the bile.

Satisfactory methods for the estimation of cholesterol have been, until recently, unavailable, and to Windaus⁶ is due the credit of introducing the first procedure for its quantitative estimation, dependent on the fact that the digitalis glucosid, digitonin, forms an insoluble compound with cholesterol, which may be filtered off and weighed. With the more extended use of colorimetric methods, the Liebermann-Burchard and Salkowski color reactions have been utilized as the basis of methods of estimating cholesterol, the former by Grigaut⁷ and the latter by Weston.⁸ Since these reactions are very delicate, they at once afforded a means of estimating the cholesterol in small amounts of blood, thus furnishing a great impetus to this type of investigation. Of the two color reactions, the Liebermann-Burchard appears to have found somewhat greater favor, although both have been extensively employed. In the case of the digitonin method of estimating the total cholesterol, saponification of the cholesterol esters is necessary, since only the free cholesterol is precipitated by the digitonin. Cholesterol esters give the color reactions as well as does the free cholesterol. This fact does not appear, however, to have been recognized until very recently, since the directions for the colorimetric estimations have invariably called for a preliminary saponification. As pointed out by Bloor,⁹ this saponification is unnecessary and the colorimetric estimation of the cholesterol thus becomes further simplified. More recently Bloor and Knudson,¹⁰ by carrying out the colorimetric determination on extracts before and after the removal of the free cholesterol with digitonin, have been able to effect a simple estimation of both the free cholesterol and its esters. Despite the advances that have been made in improving the analytical technic of estimating cholesterol in the blood, there still seems to be some question as to the reliability of the absolute values reported. This point will be discussed in connection with the method which we have employed. It is believed, however, that the data on record are sufficiently accurate to warrant, in general, the conclusions that have already been reached.

Cholesterol occurs in the blood in both the free and combined state. Free cholesterol is present in the corpuscles and to some extent in the

6. Windaus, A.: *Ztschr. f. physiol. Chem.*, 1910, **65**, 110.

7. Grigaut, A.: *Compt. rend. Soc. de biol.*, 1910, **68**, 791, 827; 1911, **71**, 513.

8. Weston, P. G.: *Jour. Med. Research*, 1912, **26**, 47; Weston, P. G., and Kent, G. H.: *ibid.*, 531.

9. Bloor, W. R.: *Jour. Biol. Chem.*, 1916, **24**, 227.

10. Bloor, W. R., and Knudson, A.: *Jour. Biol. Chem.*, 1916, **27**, 107.

plasma, and the cholesterol esters in the plasma alone. Bloor and Knudson¹¹ have found that in the whole blood the average percentage of cholesterol in combination as esters was about 33.5 per cent., and in the plasma 58 per cent. of the total cholesterol. Most of the data recorded in the literature, however, are for the total cholesterol of the blood, some of the results being on the plasma or serum, others on the whole blood. Normally, the concentration of cholesterol is nearly the same in the plasma and the whole blood, although, if anything, the plasma content is slightly higher and, pathologically, it seems to be subject to somewhat greater variations. When cholesterol or its esters are fed in solution in oil or in natural solution, as in egg yolk, the cholesterol is absorbed from the intestine through the chyle¹² and brings about an increase in the cholesterol of the blood.^{1, 13}

The normal value for the cholesterol of human blood has been regarded, until very recently, to be about 0.15 per cent. The average value found by Bloor¹⁴ for normal men was 0.21 per cent. and for normal women, 0.23 per cent. Although 0.15 per cent. is probably too low a figure, it would seem that the figures of Bloor were too high, and that possibly 0.16 or 0.17 per cent. may more nearly represent the true value for the cholesterol of human blood. Pathologically, a great many conditions have been recorded in which a hypercholesterolemia was found, while in a few conditions hypocholesterolemia has been noted. In general, it may be stated that hypercholesterolemia is found in arteriosclerosis, nephritis, diabetes, especially with acidosis, obstructive jaundice, in many cases of cholelithiasis, in the early stages of malignant tumors and in pregnancy. The chief condition in which low values for cholesterol are found is anemia. Further discussion of these pathologic variations will be taken up in connection with our own results.

As already pointed out, there appears to be some question as to the reliability of the absolute values reported in the literature for the cholesterol of the blood. It would appear that many of the results are somewhat low, owing to incomplete extraction of the cholesterol or possibly, as suggested by Bloor,⁹ to destructive action on the cholesterol of the alkali employed in the preliminary saponification. Bloor has recently suggested a method of extraction for the cholesterol which is very simple and would appear to be very complete, but the results obtained with the method are higher than those obtained with the older methods, and rather irregular, owing, apparently, to the presence in

11. Bloor, W. R., and Knudson, A.: *Jour. Biol. Chem.*, 1916, **29**, 7.

12. Mueller, J. H.: *Jour. Biol. Chem.*, 1915, **22**, 1.

13. Lehman, E. P.: *Jour. Biol. Chem.*, 1913-1914, **16**, 495.

14. Bloor, W. R.: *Jour. Biol. Chem.*, 1916, **25**, 577.

the extracts used of substances interfering with the Liebermann-Burchard color reaction. According to investigations of Luden,¹⁵ these probably result from a combination of the bile pigments and bile acids.

Our first analyses carried out in 1913 (data on pellagra, Table 8) were made according to the technic given by Autenrieth and Funk,¹⁶ but the subsequent determinations (1914-1915) were made according to the simple technic outlined later. The results with this method were uniform and compared favorably with figures given in the literature, but in carefully checking up the results, it was found that the simple extraction as carried out, was incomplete. The results, however, are comparative and it is believed sufficiently accurate to allow a discussion of the general subject.

METHOD OF ESTIMATING THE CHOLESTEROL

The technic which was employed for the estimation of the cholesterol in most of the present series of experiments, was carried out as follows:¹⁷ 2 c.c. of the oxalated blood were pipetted into a porcelain crucible of 50 c.c. capacity, 10 c.c. of 10 per cent. sodium hydroxid added, the mixture thoroughly stirred with a small glass rod and then placed over a boiling water bath for two hours to bring about the saponification of the cholesterol esters and solution of the protein material. At the end of this time about 15 gm. of plaster of Paris, were slowly added with constant stirring to prevent caking. When this was allowed to stand at room temperature over night, or placed in the drying oven at 90 F. for one hour, the mixture became a perfectly dry and very fine powder. The powder was transferred to a 250 c.c. bottle with stopper, 50 c.c. of chloroform added and the mixture thoroughly shaken for several minutes at intervals during a period of about two hours, after which the mixture was filtered into a perfectly dry cylinder or test tube through a dry filter paper. Five c.c. of this filtrate were employed for the colorimetric estimation as described later.

With the method just outlined, the extraction does not appear to be complete, the results being uniformly somewhat low (apparently about 15 per cent.). To insure complete removal of the cholesterol, a simple, continuous extractor is now employed.¹⁸ Since, as Bloor has pointed out, the cholesterol esters give the color reaction as well as the free cholesterol, saponification is unnecessary and is omitted. One c.c. of blood is pipetted into a crucible containing about 4 to 5 gm. of plaster of Paris, stirred and dried. It is now emptied into a small extraction shell (4 cm. long) and then inserted in a short test tube (2.5 by 6 cm.), in the bottom of which are a number of small holes. This is now attached to a large cork on a small reflux condenser and the tube and cork inserted in the neck of a 150 c.c. extraction flask containing about 20 to 25 c.c. of chloroform. Extraction is continued for about twenty minutes on an electric hot plate, the chloroform made up to some suitable volume, such as 20 c.c., filtered, if necessary, and colorimetric estimation carried out as described below.

Five c.c. of the chloroform extract are pipetted into a dry test tube and 2 c.c. of acetic anhydrid and 0.1 c.c. of concentrated sulphuric acid (best with a 0.1 c.c. pipette) added. After thorough mixing, the solution is placed in the dark for ten minutes to allow the color to develop. It is then compared against

15. Luden, G.: *Jour. Biol. Chem.*, 1917, **29**, 463.

16. Autenrieth, W., and Funk, A.: *München. med. Wchnschr.*, 1913, **60**, 1243.

17. Myers, V. C., and Gorham, F. D.: *The Post-Graduate*, 1914, **29**, 938.

18. The details of this method will be described in a paper to be published.

a standardized aqueous solution of naphthol green B in a Hellige colorimeter. This excellently matches the cholesterol color and appears to be permanent, whereas cholesterol solutions in chloroform quite rapidly deteriorate. The solution of the dye employed was 0.0118 per cent. Employing a standard of this colorimetric strength (practically identical with that obtained from a 0.08 per cent. chloroform solution of cholesterol), the following formula, in which R represents the colorimetric reading, may be used to compute the cholesterol in the 5 c.c. of solution employed: $103 - R \times 0.00847 = \text{mg. of cholesterol in 5 c.c. of chloroform.}$

DISCUSSION OF RESULTS

As will be found in Table 1, the cholesterol content of the whole blood of fourteen normal subjects, taken at random and not on special diet, varied from 0.13 to 0.19 per cent., with an average of 0.15 per

TABLE 1.—NORMAL SUBJECTS

Case	Age	Sex	Cholesterol of Blood, per Cent.
72 E. H.	51	♀	0.13
3 A. H.	65	♂	0.14
27 L. R.	41	♀	0.14
77 S. E.	26	♂	0.14
106 E. S.	36	♂	0.14
125 K. P.	15	♀	0.14
140 M. K.	26	♂	0.14
139 B. W.	26	♀	0.14
43 A. T.	31	♂	0.15
59 M. E.	33	♀	0.16
144 C. L.	28	♀	0.16
133 F. S.	20	♀	0.16
170 D. N.	55	♂	0.17
15 M. W.	38	♂	0.19

cent., figures which compare favorably with data reported in the literature (excepting the results of Bloor¹⁴ and Denis¹⁹). As already pointed out in connection with a discussion of the method we have employed, these figures are probably slightly low, and 0.16 or 0.17 per cent. probably more nearly represents the true average for these subjects. For comparison with our own data on pathologic cases, however, 0.15 per cent. will be considered as the average normal.

In Table 2 are collected data on ten cases showing arteriosclerosis. A tendency toward hypercholesterolemia is evident when one compares

19. Denis, W.: Jour. Biol. Chem., 1917, 29, 93. This paper gives the important literature references.

the figures with those of the normal cases given in Table 1. The figures are comparable with those given by Schmidt.²⁰ Just what relation there is, if any, between hypercholesterolemia and arteriosclerosis is not apparent. It is worthy of note, however, that histologic changes have been noted in the aorta after the experimental administration of cholesterol.²¹

In Table 3 data are recorded for the blood cholesterol on fifteen miscellaneous cases of nephritis. Most of the results obtained in these cases are quite above our normal findings. As will be noted in the

TABLE 2.—ARTERIOSCLEROSIS

Case	Age	Sex	Blood Pressure		Phthalein Output 2 Hrs., per Cent.	Cholesterol in Blood, per Cent.
			Systolic	Diastolic		
79 F. S.	66	♂	166	74	22	$\left\{ \begin{array}{l} 0.26 \\ 0.23 \\ 0.18 \end{array} \right.$
105 M. H.	71	♀	180	136	..	0.23
71 L. W.	62	♀	143	62	67	$\left\{ \begin{array}{l} 0.21 \\ 0.18 \end{array} \right.$
163 E. K.	66	♀	156	108	..	0.19
83 L. B.	64	♀	260	164	56	0.18
174 A. P.	50	♂	146	88	58	0.18
192 J. M.	55	♂	178	112	30	0.18
157 N. A.	52	♂	172	122	52	0.17
88 E. J.	58	♂	146	128	..	0.16
108 G. S.	57	♂	158	112	..	0.16

table, there is no apparent relation in this series between the cholesterol and the blood pressure or nitrogen retention. Excepting the observations of Denis,¹⁹ who found the cholesterol increased in only one case of nephritis out of a very large series, the observations recorded harmonize very well with data reported in the literature.^{20, 22}

The few observations we have made on diabetes are recorded in Table 4. Hypercholesterolemia was present in four of the eight cases, and it is of interest that it was these four cases which showed evidence

20. Schmidt, H. B.: The Clinical Study of Hypercholesterinemia. *THE ARCHIVES INT. MED.*, 1914, **13**, 121.

21. Anitschkow, N.: *Deutsch. med. Wchnschr.*, 1914, **40**, 1215; Means, J. W., and Klotz, O.: *Jour. Med. Research*, 1916, **34**, 41.

22. Chauffard, A., Laroche, G., and Grigaut, A.: *Compt. rend. Soc. de biol.*, 1911, **70**, 108; Widal, F., Weill, A., and Laudat, M.: *Semaine méd.*, 1912, **32**, 529; Bacmeister and Henes: *Deutsch. med. Wchnschr.*, 1913, **39**, 544; Klinkert, D.: *Berl. klin. Wchnschr.*, 1913, **50**, 820; Cantieri, C.: *Wien. klin. Wchnschr.*, 1913, **26**, 1692; Henes, E.: *New York State Jour. Med.*, 1915, **15**, 310.

of acidosis. Since, as pointed out by Bloor,²³ the cholesterol increases along with the other blood lipoids in diabetic lipemia, the cholesterol may be taken here as an index of the lipid content of the blood.

Considerable discussion has arisen with regard to the cholesterol content of the blood in cholelithiasis. Henes²⁴ has maintained that a

TABLE 3.—NEPHRITIS

Case	Age	Sex	Type of Nephritis	Blood Pressure		Phthal- cin Output 2 Hrs., per Cent.	Blood Uren N., Mg. to 100 C.c.	Blood Creat- inin, Mg. to 100 C.c.	Date 1914-1915	Choles- terol of Blood, per Cent.
				Sys- tolic	Diast- olic					
82 W. F.	25	♂	Mercuric bichlorid	155	70	..	219	28.1	[Nov. 13 Nov. 16 Nov. 23	0.34 0.22 0.20
81 E. E.	30	♀	Interstitial; edema	214	154	10	102	5.3	[Dec. 16 Jan. 11	0.25 0.26
12 E. B.	24	♂	Interstitial	241	116	14	Oct. 5	0.28 0.25
124 F. S.	67	♂	Interstitial	114	77	22	10	1.5	[Nov. 14 Dec. 15	0.26 0.18
113 I. D.	17	♀	Interstitial	102	130	0	209	20.0	[Dec. 21 Dec. 30 Jan. 3	0.18 0.22 0.21
111 G. F.	22	♂	Parenchym- atous	53	21	Dec. 10	0.23
160 T. D.	34	♂	Interstitial	195	120	3	66	8.3	[Jan. 15 Jan. 26 Feb. 12	0.17 0.19 0.18
138 L. R.	45	♂	Diffuse	105	125	47	24	4.2	[Dec. 26 Jan. 11	0.15 0.19
187 M. F.	52	♀	Diffuse	162	112	45	Dec. 21	0.19
204 J. B.	34	♂	Interstitial	185	95	5	49	7.2	Apr. 3 (17)	0.19
64 L. B.	64	♀	Interstitial	260	164	56	16	3.1	Dec. 28	0.18
150 L. P.	62	♂	Diffuse	185	...	0	80	4.8	Jan. 6	0.18
184 L. S.	22	♀	Parenchym- atous	148	128	22	...	3.1	Jan. 29	0.18
197 J. W.	34	♂	Interstitial	188	126	2	63	6.5	[Feb. 24 Mar. 1	0.14 0.16
205 F. R.	32	♂	Interstitial	205	120	0	102	11.5	Apr. 2 (17)	0.15

hypercholesterolemia is almost invariably found in cases of cholelithiasis without fever. He has suggested that the hypercholesterolemia is the fundamental and primary etiologic factor in the formation of gallstones. In a more recent discussion of the subject, Rothschild and

23. Bloor, W. R.: Jour. Biol. Chem., 1916, 26, 417.
24. Henes, E.: Jour. Am. Med. Assn., 1914, 63, 146; Surg., Gynec. and Obst., 1916, 23, 91.

TABLE 4.—DIABETES

Case	Age	Sex	Cholesterol of Blood, per Cent.	Urine		Blood Sugar, per Cent.	CO ₂ Combining Power of Blood (Van Slyke)
				Acetone	Diacetic Acid		
180 R.	52	♀	0.22	+	+		
			0.18	+	—		
			0.18	+	—		
			0.19	+	—		
192 M. McO.	52	♀	0.19	+	+		
195 B. L.	..	♂	0.21	+	+		
191 D. W.	55	♂	0.16	—	—		
198 M. W.	..	♂	0.15	—	—		
207 H. R.	..	♂	0.35	0.30	34
208 M. B.	25	♀	0.14	0.16	54
206 V. A.	45	♂	0.11	0.25	50

TABLE 5.—CHOLELITHIASIS

Case	Age	Sex	Jaundice	Time of Specimen	Cholesterol in Blood, per Cent.	Remarks
22 H. O.	44	♀	None	Anteoperation	{ 0.13 0.13 }	Cholesterol stones found at operation
				Postoperative 2 and 3 weeks	{ 0.16 0.17 }	
36 G. K.	52	♂	None	Anteoperation	0.13	Cholesterol stones found at operation
162 V. O'Z	52	♀	None	Anteoperation	0.14	Cholesterol stones found at operation
				Postoperation	0.16	
200 M. L.	33	♀	Slight	0.17	Cholesterol stones found at operation
173 W. L.	15	♀	None	Anteoperation	0.18	Many cholesterol stones
				Postoperation	0.21	
2 A. R.	63	♀	Slight	{ 0.21 0.18 }	No operation
4 E. F.	43	♀	Present	0.22	No operation
68 M. J.	40	♀	None	0.16	No operation
69 M. L.	44	♀	None	0.18	No operation
98 R. S.	42	♂	Marked	0.22	No operation

Rosenthal,²⁵ while admitting that many cases of gallstones show a hypercholesterolemia, point out that the exceptions are manifold, and that in their own series of thirty-seven cases, about a third did not show an increase in the cholesterol of the blood at the time the exam-

25. Rothschild, M. A., and Rosenthal, N.: Am. Jour. Med. Sc., 1916, **152**, 394.

ination was made. These authors emphasize the fact, however, that in a certain group of cases the hypercholesterolemia is very persistent and operation affords only temporary relief. They believe that properly selected diets (low in cholesterol) have been very beneficial in these cases.

It is not possible to draw conclusions from our own limited series of ten cases (Table 5). It will be noted, however, that only one of the five cases confirmed by operation showed a hypercholesterolemia, while in the remaining five cases those patients showing an increased blood cholesterol were jaundiced. The apparent influence of jaundice is shown in Table 6.

TABLE 6.—JAUNDICE

Case	Age	Sex	Type of Jaundice	Cholesterol of Blood per Cent.
87 F. T.	21	♂	Catarrhal.....	0.21
97 R. W.	23	♂	Catarrhal.....	0.19
110 R. K.	51	♂	Obstructive.....	0.29
131 J. N.	53	♂	Obstructive.....	{ 0.17
				{ 0.18
99 A. H.	42	♂	Obstructive.....	0.16
107 O. R.	22	♂	Syphilitic.....	0.10

TABLE 7.—MALIGNANCY

Case	Age	Sex	Location of Growth		Hemoglobin (Sahli) per Cent.	Cholesterol in Blood, per Cent.
152 H. H.	47	♂	Stomach.....	Early	80	0.20
29 G. P.	43	♀	Stomach.....	Early	78	0.18
109 H. M.	53	♂	Esophagus.....	Early	90	0.18
14 I. L.	45	♂	Vertebrae.....	Early	90	0.18
5 R. M.	51	♀	Stomach.....	Early	85	0.17
57 H. F.	58	♂	Stomach.....	Early	86	0.15
46 N. K.	34	♀	Colon.....	Early	..	0.14
148 O.	50	♂	Pancreas.....	Late	..	0.16
56 E. K.	62	♂	Stomach.....	Late	..	0.13
135 H. H.	57	♂	Stomach.....	Late	72	0.13
102 A. O.	62	♀	Pancreas and stomach..	Late	59	0.13
31 G.	44	♂	Stomach.....	Late	70	0.12
37 H. A.	56	♂	Stomach.....	Late	68	0.12
40 F. M.	37	♀	Esophagus.....	Late	65	0.12
67 M. L.	45	♂	Stomach.....	Late	80	0.12

From our own data on malignancy it would appear that among the early cases the blood cholesterol was normal or slightly above normal, while in the late cases the figures were somewhat below normal. This, in general, is the conclusion that has been reached by other workers.²⁰

TABLE 8.—PELLAGRA

Case	Age	Sex	Severity of Condition	Cholesterol of Blood Serum, per Cent.
1 J. H.	45	♂	Mild	0.27
2 D. G.	23	♀	Moderately severe	0.24
3 J. O.	42	♀	Mild	0.21
4 J. S.	29	♀	Moderately severe	0.20
5 E. O'N.	32	♀	Moderately severe	0.18
6 E. B.	25	♀	Mild	0.18
7 S. E.	28	♀	Moderately severe	0.17
8 M. T.	19	♀	Moderately severe	0.13

TABLE 9.—SYPHILIS

Case	Age	Sex	Stage of Syphilis	Wassermann	Cholesterol of Blood, per Cent.	Remarks
24 N. G.	42	♀	I	Positive	0.17	
74 A. G.	20	♂	I	Positive	0.14	
142 O. D.	26	♀	I	Positive	0.13	
25 L. D.	33	♀	II	Positive	0.14	
32 C. C.	24	♀	II	Positive	0.12	
107 O. R.	22	♂	III	Positive	0.19	Congenital
17 L. C.	46	♂	III	Positive	0.17	
18 L. K.	25	♂	III	Positive	0.15	Gonorrheal arthritis
63 H. D.	25	♀	III	Positive	0.15	
91 M. C.	36	♀	III	Positive	0.15	
26 Z. K.	34	♀	III	?	0.15	
133 W. L.	48	♂	III	Positive	0.14	Aneurism
93 P. L.	27	♂	III	Positive	0.14	
147 S. S.	55	♂	III	Positive	0.13	
136 E. O.	28	♂	III	Positive	0.12	General paresis

Our cases of pellagra, the analyses of which were made in 1913, according to the technic of Autenrieth and Funk using a Duboscq colorimeter, show, with one exception, a tendency toward a hypercholesterolemia.

26. Luden, G.: Jour. Lab. and Clin. Med., 1916, 1, 662.

lemia. It is of interest in this connection, according to the observations of Fischl,²⁷ that the cholesterol content of the blood is high in the ordinary dermatoses not accompanied by fever.

The data which we have collected in Tables 9, 10 and 11 on syphilis, gastro-intestinal conditions and miscellaneous conditions, require com-

TABLE 10.—GASTRO-INTESTINAL CONDITIONS

Onse	Age	Sex	Diagnosis	Cholesterol in Blood, per Cent.
5 M.	51	♀	Gastric ulcer	0.17
127 S. S	44	♀	Gastric ulcer	{ 0.13 0.17
86 A.	48	♀	Gastric ulcer	0.14
91 O.	36	♀	Gastric ulcer	0.15
118 A. K.	41	♀	Gastric ulcer	0.14
154 P. K.	35	♂	Duodenal or gastric ulcer	0.16
55 D.	29	♂	Duodenal ulcer	0.17
134 H. K.	38	♂	Duodenal ulcer	0.17
30 G.	45	♂	Duodenal ulcer	{ 0.16 0.13
101 B. D.	34	♂	Duodenal ulcer	0.14
180 A. K.	37	♂	Duodenal ulcer	0.14
104 I. O.	62	♀	Colitis	0.18
58 F. S.	..	♀	Colitis	0.16
38 M. B.	27	♀	Colitis	0.14
90 D.	39	♀	Colitis	0.13
123 E. B.	19	♀	Colitis	0.13
129 R. B.	32	♀	Colitis	0.13
8 F. S.	47	♀	Colitis	0.12
119 H. S.	17	♂	Typhoid fever { 18th day 28th day	{ 0.17 0.18
6 K.	29	♂	Typhoid fever { 28th day 42d day	{ 0.13 0.16
7 R. L.	28	♂	Typhoid fever, 25th day	0.15
9 S. S.	51	♀	Typhoid fever, 33d day	0.14
33 E. W.	16	♂	Typhoid fever, 23d day	0.18

paratively little comment, since, with a very few exceptions, they are essentially all within normal limits. It may be noted in Table 11, however, that a hypercholesterolemia was found in two cases, one a case

27. Fischl, F.: Wien. klin. Wchnschr., 1914, 27, 982.

TABLE 11.—MISCELLANEOUS CONDITIONS

Case	Age	Sex	Diagnosis, Remarks	Cholesterol in Blood, per Cent.
96 H. D.	45	♂	Acute alcoholism	0.14
44 P.	53	♂	Chronic alcoholism	{ 0.13 0.13
64 W. L.	32	♂	Chronic alcoholism	0.17
126 W	34	♂	Asthma	0.15
47 H. H.	32	♂	Acromegaly	{ 0.14 0.14 0.16
78 R. O.	52	♂	Lymphatic leukemia	0.17
188 E.	33	♂	Mycogenous leukemia; fever	0.13
144 E. M.	54	♀	Lobar pneumonia	0.14
13 J. B.	57	♂	Gout	0.14
39 M. P.	47	♀	Gout	0.17
57 L. M.	19	♂	Brain tumor	0.16
18 L. O.	25	♂	Arthritis; syphilis	0.13
50 R.	40	♂	Chronic arthritis	0.12
122 A. R.	14	♀	Chronic arthritis	0.14
112 M. L.	17	♀	Chronic arthritis	0.16
187 A. M.	43	♀	Chronic arthritis	0.18
16 J. W.	12	♂	Trachoma	0.15
75 C. C.	16	♂	Imbecility	0.11
136 E. O.	28	♂	General paresis	0.12
52 R. C.	23	♀	Pregnancy, 9 months	0.18
60 L. S.	34	♀	Pregnancy, 8 mo.; eclampsia	0.23
40 F. M.	37	♀	Pregnancy, 3 mo.; malignancy	0.12
179 D	24	♀	Pregnancy, 6 months	0.13
1 J. J.	34	♂	Cirrhosis of liver, hypertrophic	0.14
21 K	28	♂	Cirrhosis of liver, alcoholic	0.17
44 P.	53	♂	Cirrhosis of liver, atrophic	{ 0.13 0.13
19 B. O.	53	♂	Miliary tuberculosis; temp. 105 F.	{ 0.26 0.27*
34 D.	35	♂	Pulmonary tuberculosis	0.14
73 C. D.	40	♂	Tuberculosis of glands of neck	0.14
132 J. E.	42	♂	Pulmonary tuberculosis	0.15
117 H. C.	36	♀	Pulmonary tuberculosis	0.16
143 L. S.	42	♂	Pulmonary tuberculosis	0.16
163 F. L.	14	♂	Tuberculous peritonitis	0.18

* Serum.

of pregnancy with eclampsia, and the other a case of miliary tuberculosis with fever.

That the cholesterol of the blood is lowered in anemia has been recognized for some time. The problem has already received considerable attention at the hands of Italian investigators, notably Antonelli²⁸ and Cantieri.²⁹ Cantieri noted beneficial effects after the administration of therapeutic doses of cholesterol ester, although there was little influence on the cholesterol of the blood serum. In her recent paper, Denis¹⁹ noted subnormal values in primary and secondary anemias. She was unable to find any definite relation between the number of corpuscles or hemoglobin percentage and the cholesterol values.

TABLE 12.—PERNICIOUS ANEMIA

Case	Age	Sex	Hemoglobin (Sahl) per Cent.	Red Blood Cells	Cholesterol, per Cent.
61 J. H.	54	♂	46	2,140,000	0.061 whole blood
			44	2,030,000	{ 0.052 whole blood 0.017 plasma 0.15 washed cells
165 O. G.	48	♂	40	2,368,000	1/28/15 { 0.07 whole blood 0.065 plasma 0.12 washed cells
			20	1,120,000	2/10/15 { 0.075 whole blood 0.07 plasma 0.13 washed cells
			..	1,200,000	2/17/15 { 0.072 whole blood 0.065 plasma 0.13 washed cells
182 F. S.	50	♂	34	2,080,000	3/24/15* { 0.056 plasma 0.14 washed cells
			25	660,000	4/3/17 0.06 whole blood

* Day of splenectomy.

Our observations on pernicious anemia are given in Table 12. The finding of very low values for the cholesterol of the plasma, with essentially normal figures for the cells, would appear to be of considerable interest in this condition in view of the antihemolytic influence of cholesterol. For this reason we attempted to increase the content in the blood by feeding cholesterol to patient F. S., but as yet our data are insufficient to draw conclusions. It might be noted, however, that although there was no apparent increase in the blood cholesterol, there seemed to be some clinical improvement, in harmony with the findings of Cantieri. An interesting problem naturally suggests

28. Antonelli, G.: Policlinico, Rome, 1914, **21**, 341.

29. Cantieri, C.: Rassegna di clin., terap. e sc. affini, August, 1914, abstr., Zentralbl. Biochem. u. Biophys., 1915, **18**, 184.

itself as to the absorbability of cholesterol and other lipoids in anemias of the pernicious type. This general problem is being further investigated by one of us (G).

SUMMARY

Cholesterol estimations were made in the blood of about 200 patients, suffering clinically from about twenty-five different diseases. Hypercholesterolemia was observed, though not invariably, in arteriosclerosis, nephritis, obstructive jaundice and diabetes. A hypocholesterolemia was found in the cachexia of malignancy and all anemias of the pernicious type. The low cholesterol values encountered in the blood plasma of patients with pernicious anemia are regarded as of considerable significance, especially in view of the strong antihemolytic action of cholesterol. The findings in cholelithiasis were quite inconsistent. Since hypercholesterolemia may be found in many conditions and is not uniformly constant in cholelithiasis, it would seem that the blood cholesterol possessed only a limited diagnostic usefulness in this condition. The estimation may possess some diagnostic value in diabetes, since the cholesterol serves as an easily determined index of any lipemia.

Humboldt Building—303 East Twentieth Street.

THE TEMPERATURE METHOD IN THE LOCALIZATION OF A CARDIAC PACEMAKER *

BENJAMIN H. SCHLOMOVITZ, M.S.
CHICAGO

AND
C. S. CHASE, M.D.
IOWA CITY, IOWA

INTRODUCTION

The present study was undertaken to determine possible influences on the cardiac rhythm of heating remnants of the original sinus venosus tissue in the right auricle and neighboring parts other than the sino-auricular node. We have attempted in this work to control accurately the temperature, time of application and definite delimitation of the area affected. The work, in part, is also a critical analysis of this method of localization of a primary cardiac pacemaker, in view of the fact that in many previous studies of this character such accurate controls were not observed.

HISTORICAL

The method of accurate control of the temperature for localizing automatic tissue in the heart has not, so far as we are aware, been emphasized in any previous work. This method has been employed extensively by a number of investigators for localization of the primary pacemaker (MacWilliam,¹ Engelmann,² Adam,³ Ganter and Zahn⁴); and for determination of variations in the seat of impulse formation under the influence of temperature changes within or outside the normal seat of impulse initiation (Jaeger,⁵ Hering and Koch,⁶ Flack,⁷ Brandenburg and Hoffman,⁸ Ganter and Zahn,⁹ Zahn,¹⁰ Meek and Eyster,¹¹ Lewis¹²). Finally, it has been used to determine the relation of the extrinsic cardiac nerves to the system of nodal tissues of the heart (Clark,¹³ Flack,⁷ Schlomovitz, Eyster and Meek¹⁴) and hinted at by Stewart.¹⁵

* Submitted for publication May 2, 1917.

* From the Departments of Pharmacology, State Universities of Illinois and Iowa.

1. MacWilliam: *Jour. Physiol.*, 1888, **9**, 175 and 389.
2. Engelmann: *Arch. f. d. ges. Physiol.*, 1896, **65**, 109.
3. Adam: *Arch. f. d. ges. Physiol.*, 1906, **111**, 607.
4. Ganter and Zahn: *Arch. f. d. ges. Physiol.*, 1912, **145**, 335 and 392.
5. Jaeger: *Deutsch. Arch. f. klin. Med.*, 1910, **100**, 1.
6. Hering and Koch: *Arch. f. d. ges. Physiol.*, 1910, **136**, 466.
7. Flack: *Jour. Physiol.*, 1910, **41**, 64.
8. Brandenburg and Hoffman: *Med. Klinik.*, 1912, **8**, 16.
9. Ganter and Zahn: *Arch. f. d. ges. Physiol.*, 1913, **154**, 492.
10. Zahn: *Arch. f. d. ges. Physiol.*, 1913, **151**, 247.
11. Meek and Eyster: *Am. Jour. Physiol.*, 1914, **34**, 368.
12. Lewis: *Heart*, 1914, **5**, 247.
13. Clark: *Jour. Physiol.*, 1912, **44**, 169; *Heart*, 1913, **4**, 379.
14. Schlomovitz, Eyster and Meek: *Am. Jour. Physiol.*, 1915, **37**, 177.
15. Stewart: *Physiology*, Ed. 7, 1914, p. 158.

In a previous communication¹⁶ we suggested that changes in cardiac rate may result from the application of heat to certain areas other than the seat of impulse initiation if the temperature is sufficiently high to increase the automaticity of these regions, and thus lead to possible erroneous conclusions as to the seat of the pacemaker as determined by this method. It would seem, therefore, of essential importance in the localization of the pacemaker by this method that the temperature range employed should not exceed or fall below the temperature of the tissue to such an extent as to affect extensive variations in the automaticity of the region affected and possible removal of the seat of impulse formation. This fact stood out clearly in our study¹⁶ on the origin of the cardiac impulse in the turtle. More recently Eyster and Meek¹⁷ have noted the inferiority of the temperature method as hitherto employed to the electrical method.

The idea that the pacemaker can shift from one position to another was an essential influence in carrying on the work reported. Gaskell was the first to emphasize a localized origin of the heart beat, and that the seat of this localization could be removed to other regions under certain conditions. The work of Gaskell, Engelmann, Lohman and others has shown that this may occur in one or both of two ways, either by depression of the automaticity within the normal pacemaker, or, in certain cases, by increase of inherent but dormant automaticity in other regions. So far at least as the mammalian heart is concerned, most workers believe that under all approximately normal conditions the pacemaker, even when removed from its normal seat, always resides within some part of the system of nodal tissues (Ganter and Zahn, Zahn, Meek and Eyster¹⁸).

METHODS

Six animals were experimented on—four dogs (puppies), one cat, and one rabbit. Ether was administered, and the thorax was opened under artificial respiration. The phrenic nerves were cut and the pericardium sewed back. A ligature inserted in the adipose tissue of the a-v groove was used to pull the heart gently to the left, thereby exposing the region of the great veins and right auricle. The exposure was similar to that shown by Brandenburg and Hoffman.⁸ A receiving tambour connected by air transmission to a recording tambour received the auricle movements, the rate, from the appendix of the right auricle. A normal record was taken, and then a thermode was applied to a particular spot for a definite time interval. The heart, if influenced, was permitted to return to normal, and the thermode was again placed at the same or at a different spot. As a rule, the return to normal occurred immediately on removal of the thermode, or continued for several beats, never more than ten or fifteen, which was exceptional. This procedure was kept up until the end of the experiment. The copper tip C (Fig. 1) which was made from a bullet is 5 mm. long, and 1 mm. wide. One end of the tip was filed down giving an area of 1 square millimeter, which could be applied to heart tissue by holding the thermode at an angle.

Two ranges of temperature above body temperatures were used, a low range

16. Schlomovitz and Chase: *Am. Jour. Physiol.*, 1916, **41**, 112.

17. Eyster and Meek: *THE ARCHIVES INT. MED.*, 1916, **18**, 796.

18. Meek and Eyster: *Heart*, 1914, **5**, 227.

and a high range, relatively. The various spots warmed are shown in Figure 2. It is possible that we were not always successful in applying the thermode in the coronary sinus, thereby reducing our results at that point.

In most cases the thermode was applied for five seconds, in some instances ten seconds, and in those instances in which the area comprising the head of the S-A node revealed unusual responsiveness, the thermode was kept there only one to three seconds. A stop watch was used to check the time during which the thermode was applied.

A control of our method seems to have been satisfied by the following considerations: The point VI was chosen because it has no specialized tissue. A rabbit was used in one experiment because the specialized tissue in its heart is in much more appreciable amount close to the inferior vena cava along the taenia terminalis, while in the other

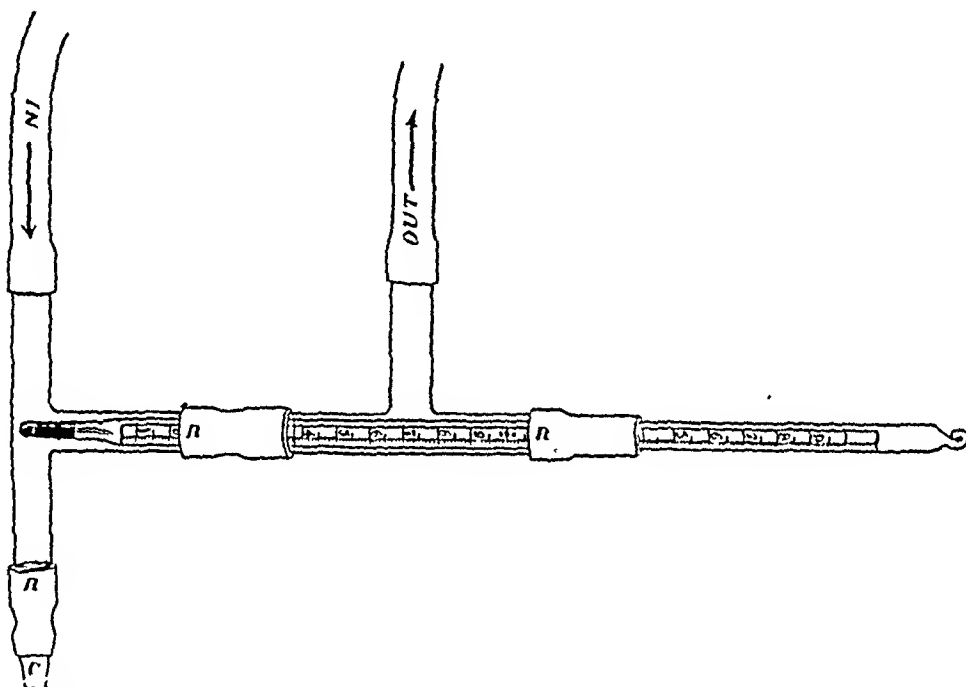


Fig. 1.—Thermode. C, copper tip; R, rubber tube; In, inflow; Out, outflow.

animals used the nodal tissue is most concentrated close to the angle formed by the right auricle and the termination of the superior vena cava. Therefore, in the rabbit the response at III should be marked, and this was found to be true. A probe, at room temperature, was applied at II (the spot most responsive) to see what effect a cooler object and especially irritation had. Spot II, known to be the position of the S-A node was found to be the spot at which rhythmicity could be influenced most easily.

The position and extent of the sino-auricular node, auriculo-ventricular node and associated structures have been so fully described by Keith and Flack,¹⁹ Koch,²⁰ Lewis, Oppenheimer and Oppenheimer,²¹

19. Keith and Flack: Jour. Anat. and Physiol., 1907, **41**, 172.

20. Koch: Deutsch. med. Wchnschr., 1909, **35**, 429; Verhandl. d. Deutsch. Path. Gesellsch., 1909, **13**; Med. Klin., 1911, **7**, 447; 1912, **8**, 108; Arch. f. d. ges. Physiol., 1913, **151**, 297.

21. Lewis, Oppenheimer and Oppenheimer: Heart, 1910-1911, **2**, 147.

and others, that we have considered microscopic controls in our experiments as unessential.

A more accurate control of the two ranges of temperature could have been obtained by measurement of the temperature of the blood within the right auricle by means of a thermometer introduced through the azygos vein and superior vena cava. This we hope to do in subsequent experiments of this type, as well as in a series of atropinized animals.

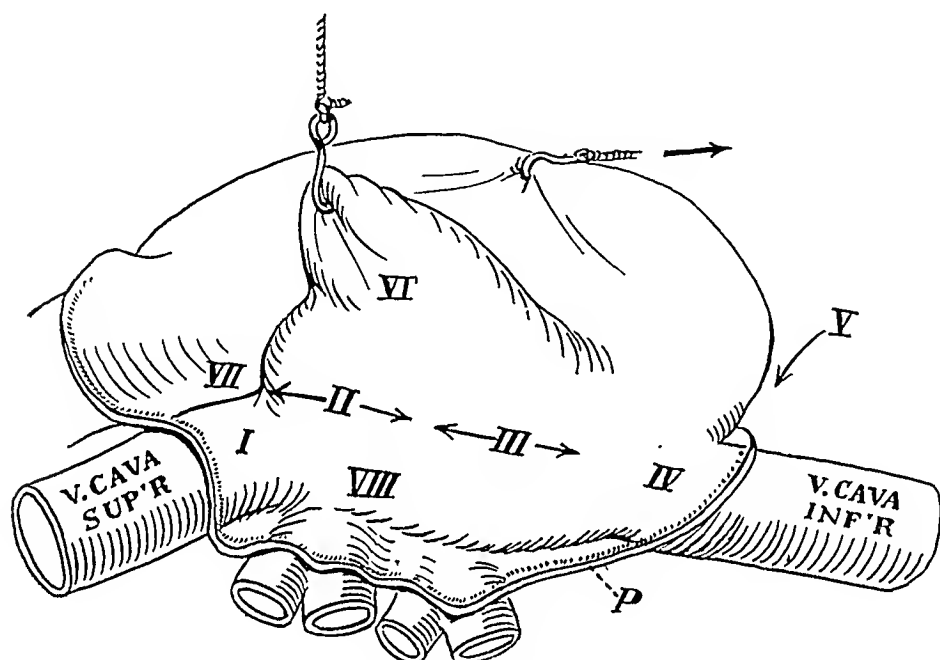


Fig. 2.—The numbers indicate where the thermode was applied. Diagrammatic sketch.

I is made up of the anterior and right lateral portions of the sup. vena cava just before it empties into the auricle.

II is the area comprised in the right border of the upper half of the sulcus terminalis; the sinus nodal tissue proper.

III is the portion on the right border of the lower half of the sulcus terminalis adjacent to the inferior vena cava.

IV is the right lateral and anterior portion of the inferior vena cava just before it empties into the auricle.

V is part of the tissue covering the coronary sinus (the auricular portion of the A-V node).

VI lies in the main body of the right auricle.

VII is that termination of the superior vena cava which forms an angle with the auricle.

VIII is on the auricular tissue adjacent to the pericardial attachment below the termination of the superior vena cava.

In the rabbit the right superior caval vein was used.

RESULTS

Analyses of Experiments.—Table 1 is a summary of the procedures and results in a single experiment (F) on a dog.

TABLE 1.—SUMMARY OF PROCEDURES AND RESULTS IN EXPERIMENT F

No. of Tracing	Point at Which Thermode Was Applied	Temperature of Thermode, C.	Heart Rate		Percentage Increase in Rate
			Before Applying Thermode	After Warming	
1	Normal	..	180		
2	II	47	180—	240	33.4
3	III	47	190	185	—3.0
4	I	47	180	180	0.0
5	VII	47	195	200	3.0
6	II (3, 4)	47	180	200	11.0
7	II	47	180	220	22.0
8	VIII	47	185	175	—6.0
9	IV	47	170	170	0.0
10	V	47	170	180	6.0
11	VI	47	170	170	0.0
12	II	47	180	200	11.0
13	III	47	180	180	0.0
14	VII	47	175	180	3.0
15	IV	47	165	165	0.0
16	VI	47	160	160	0.0
17	V	47	160	160	0.0
18	VIII	47	160	160	0.0
19	II	46	160	200	25.0
20	IV	66	160	170	6.0
21	IV	71	160	175	9.0
22	IV	73	160	160	0.0
23	III	72	160	170	6.0
24	II (3, 4)	70	150	225	50.0
25	I	71	160	160	0.0
26	VII	71	150	150	0.0
27	II (3, 4)	70	145	225	55.0
28	II (3, 4)	66	155	220	42.0
29	II (3)	70	160	180	12.5
30	IV	65	140	150	7.0
31	V	68	150	150	0.0
32	III	66	150	150	0.0
33	VII	71	145	150	3.0
34	I	73	150	150	0.0
35	II	73	150	240	60.0
36	VI	71	150	140	—7.0
37	II (probe)	Room	140	140	0.0

TABLE 1.—SUMMARY OF PROCEDURES AND RESULTS IN EXPERIMENT F

No. of Tracing	Point at Which Thermode Was Applied	Temperature of Thermode, C.	Heart Rate		Percentage Increase in Rate
			Before Applying Thermode	After Warming	
38	III	70	140	140	0.0
39	VIII	72	150	150	0.0
40	IV	66	150	145	-3.0
41	IV	74	140	140	0.0
42	V	74	140	140	0.0
43	VI	72	140	140	0.0
44	VII	72	140	145	3.0
45	I	73	145	140	-3.0
46	VIII	73	140	140	0.0
47	VIII	74	140	150	7.0
48	IV	72	140	140	0.0
49	II	72	140	180	28.0
50	(5, 6)	74	140	184	31.0
51	I	44	135	170	26.0
52	III	42	140	150	7.0
53	I	43	125	130	4.0
54	VII	43	130	130	0.0
55	IV	42	130	130	0.0
56	V	43	130	130	0.0
57	VI	43	125	130	4.0
58	III	43	130	130	0.0
59	II	42	140	170	21.0
60	(5, 6)	42	140	180	28.0
61	II (probe)	Room	Slight slowing	...	—
62	IV	72	125	130	4.0
63	IV	79	130	130	0.0
64	V	80	0.0
65	III	80	120	150	25.0
66	VIII	79	120	140	16.0
67	I	82	120	170	41.0
68	VII	82	120	140	16.0
69	V	82	120	120	0.0
70	II	82	110	160	45.0
71	VI	82	140	140	0.0
72	IV	80	140	140	0.0
73	II	79	135	180	33.0
74	Normal	..	130		

TABLE 2.—ANALYSIS OF DATA AFTER BEING TABULATED AS IN TABLE 1

No. of Experiment	Point Warmed	Average Increase in per Cent. Over Normal		Highest Individual Increase in per Cent. Over Normal		Remarks
		Low Range	High Range	Low Range	High Range	
A	I	4	12	9	77	Cat, 3/10/10
	III	2	12	6	16	
	IV	0	9	0	16	
	V	3	—	7	—	
B	I	4	3	12.5	12.5	Dog
	III	0	8	0	17	
	IV	0	1	0	5	
	V	0	0	0	—	
	VII	0	—	0	11	
	VIII	0	0	0	0	
C	I	0	11	0	20	Rabbit
	III	18	45	57	50	
	IV	3	3	4	9	
	V	6	10	5	10	
	VII	14	28	14	28	
	VIII	5	6	10	12.5	
E	I	9	10	10	29	Dog
	III	2	11	10	27	
	IV	1	24	5	46	
	V	0	23	0	35	
	VII	14	10	48	14	
	VIII	1	6	5	20	
F	I	2	9	4	41	Dog
	III	3	8	10	25	
	IV	0	2	0	10	
	V	2	0	0	0	
	VII	2	5	3	16	
	VIII	3	5	6	16	
D	I	3	23	6	48	Dog *
	III	3	13	10	40	
	IV	7	3	8	14	
	V	0	4	0	8	
	VII	13	25	11	70	
	VIII	0	16	0	42	

* Pacemaker at S-A node up to 52 then heating had only slight effect at II, while a marked effect was obtained at IV and VII. After 52, the superior vena cava assumed power of contractility, beating, as it appeared to us, synchronously with the auricle. The heart rate was one-half of the normal rate, showing that the pacemaker was in the A-V bundle, but sinus tissue exclusive of the S-A node showed that it could assume impulse initiation.

Table 2 was compiled by analyzing the data for each experiment as in Table 1, and shows the increase of the rate per cent. over the normal produced by warming with the thermode, and using the low range and high range, respectively. This table is significant in that it shows increases at points outside of the S-A node at the same or lower temperatures used by other workers. Experiment E is especially striking.

Table 3 is a summary of part of Table 2 showing those points in each experiment where increases in rate were produced.

TABLE 3.—SUMMARY OF INCREASES SHOWN IN TABLE 2

Experiments	Points on Spots Warmed							
	I	II	III	IV	V	VI	VII	VIII
A Cat.....	+	*	0	0	—	00	—	—
B Dog.....	0	*	+	0	0	00	—	0
C Rabbit.....	+	*	*	0	0	00	+	0
D Dog.....	+	*	+	0	0	00	+	+
E Dog.....	+	*	+	+	+	00	0	+
F Dog.....	+	*	+	+	0	00	+	+
Totals (18)....	5	*	4	2	1	00	3	3

The table shows where increases in rate were produced by the use of the wider range of temperature. The stars indicate marked effectiveness at the sinus node. The double zeros show that absolutely no effect was produced on the auricle. The plus marks indicate that the heart rate was increased by warming at those points. The dashes indicate that that spot was not warmed in that particular experiment.

TABLE 4.—SUMMARY OF CERTAIN DATA OF THE EXPERIMENTS

Items	Experiments						Remarks
	A	B	C	D	E	F	
1. Heart rate per min.: Beginning of experiment.....	195	220	200	180	200	180	General decrease, never an abrupt drop
End of experiment...	160	160	230	140	120	130	
2. Warming at Spot VI	0	0	0	0	0	0	Auricle; no specialized tissue
3. Warming at Spot II given in per cent. increase	50	50	90(II) 57(III)	45	100	60	Always markedly positive
4. Temperature used, 1 shown in 2 ranges: 2 low (1, 3) 3 high (2, 4) 4	52.5-64.5 67-80 50-63	53-55 60.5-79 52-54	50.5-52 61-74 52-53	50-55 70-79	37-55 56-75 42-47.5 70-74	46-47 65-74 42-44 72-84	
5. Pacemaker throughout experiment at sinus node	Yes	Yes	Yes	Yes	Yes	Yes	Shown by its responsiveness

Table 4 summarizes the following data: (a) heart rate at beginning and end of experiments; (b) the fact that no change was produced by warming Spot VI which is auricular tissue; (c) the highest individual increase in per cent. produced at Spot II which is just over the head of the sino-auricular node; (d) the temperatures of the two ranges; and (e) the fact that the pacemaker remained at the sinus node as far as we could tell.

An examination of Table 3 will show that Spot II (on the sino-auricular node) was influenced by warming in such a way as to increase the auricular rate in all experiments. The next most effective region was Area I (termination of the superior vena cava); while the other regions were only influenced in half or less than half of the experiments. Spot VI (body of the right auricle) gave no reaction in any of the experiments.

At no time did we obtain an irregular heart by our method as far as we could tell. In a number of instances the heat increased the auricular rate so much that the ventricle did not follow with each impulse. In one case the sino-auricular node was eliminated by excessive heat, and the cardiac rate dropped to one-half of that existing previously.

The Efficiency of the Thermode.—The cardiac tissue is probably never heated up to the temperature point of the thermode in an interval of five seconds, and the same holds true for an interval of ten seconds. The particular area touched by the thermode absorbs heat, and it would be interesting to know how much of an increase in the temperature of a spot, as well as the amount of heat conducted to it, would be required to produce a certain increase in rate. To obtain an approximate idea of how much heat the thermode did convey we applied it to a thermometer with a long mercury bulb for five and ten second intervals. Briefly the results were as follows:

With a room temperature of 25 C., and a thermode temperature ranging from 46 to 73.5 C., the thermometer X showed an increase in temperature of 1 to 12 C., when its initial temperature ranged from 23.5 to 30 C. The greatest increases occurred with the thermode at the higher temperatures. Example: A thermode with a temperature of 43.5 C. raised the reading of thermometer X from 25.6 to 26.8 C. when applied for five seconds. This is an increase of 1.2 C. There is no doubt that this is a different proposition than when warming tissue covered with a film of moisture with an ever-changing blood supply, continuous cellular variations, and shielded by a thin layer of visceral pericardium. It is well known that the blood supply of the sinus tissue is very abundant. The probability is that with the low range temperature the sinus tissue was seldom raised above 1 to 2 degrees centigrade.

Certainly not enough heat was absorbed to be destructive. This was sufficiently indicated by the responsiveness of the S-A node, as well as the immediate or rapid return to normal rate.

DISCUSSION

Analysis of the Method.—One of the methods employed to determine the site of origin of the cardiac impulse in the warm-blooded heart was to warm circumscribed areas of the cardiac tissue. The temperatures employed ranged from 40 to 60 C. In a number of instances the temperatures are not stated. The time of application has also varied and in most cases is not stated. In Adam's tracings this time is shown to be from 12 to 50 seconds. As a result of this method the following data have been obtained:

MacWilliam,¹ on applying slight heat locally to the terminal part of the vena cava superior, obtained a marked acceleration in the rhythm of the whole heart, while a similar slight local cooling of the ventricular apex or any part of the ventricular substance gave no change in the cardiac rate. Adam,³ working with this method before the sinus node was discovered, showed that the region most easily influenced is between the vena cavae, and that no results were obtained by warming or cooling the veins. Flack⁷ reported that the normal dominating rhythm can be affected only at the S-A node. Ganter and Zahn⁴ (p. 392) in a preliminary report state that every portion of the S-A node shares in the initiation of a normal heart beat. Koch discussed their report and said that the following seemed to him to be especially interesting, namely, that only the specialized tissue, the S-A node, manifests an influence on heart activity, while, on the other hand, influencing nearby tissue thermically, for example, the sinus remnant in the terminations of the large veins or auricle very close to the S-A node produced no typical effect on cardiac activity. Ganter and Zahn later published their experimental findings. If their sketches are compared with ours it will be seen that their points 1 to 5 correspond to our points II, III and VII (Fig. 2). They obtained an increased rate, especially at 1, 2 and 3 (equivalent to our VII and II). We obtained an increased rate at these points and at III and VII, especially when a higher temperature was used. They state again and again that at all other points warming and cooling had no influence. By systematic search they found the circumscribed spot known as the sinus node at which temperature stimuli produced a change in rate. Brandenburg and Hoffman⁵ announced practically identical results at about the same time.

That such results are not due to conduction of temperature through the tissues has been shown by Engelmann, by Ganter and Zahn, by Schlomovitz and Chase,¹⁶ and by us in the present paper. For example, in Experiment E, a temperature of 73 C. at points VI produced no

effect. So high a temperature certainly should secure response if this criticism is valid. Aschoff asserted that the indirect temperature effects in vessels supplying specialized tissue is of little importance, mainly because the same results are obtained with surviving hearts.

The above review reveals the citation of an unequivocal statement that only when heat is applied directly to the sino-auricular node can the rhythm be influenced (excluding the A-V system). A recital of a few facts will show, however, that the statement, with possible exception of that of MacWilliam, is not inclusive enough without a more careful qualification of the temperature in degrees, the tissue affected, or the time required to warm it. For example, this apparent contradiction has given rise to Erlanger's²² criticism of the temperature method, in that it gives results that seem inconstant, for by it the rate of the heart may be affected over the terminal portion of the superior cava, over the node and near the inferior cava. The results are, however, consistent in this respect, namely, that they have been obtained only within the limits of the sinus reuniens. This statement, when analyzed, involves a criticism of the findings of all the workers following MacWilliam, and the fact also that in the rabbit a marked effect is obtained close to the inferior vena cava. MacWilliam specifies "slight heating" in one place without telling how the heat was produced and "hot galvanocautery" in another paper. To say "slight heating" is insufficient. The exact temperature and the exact period of its use should have been given. It is well known that when temperature reaches about 45 C. the quality of sensation is noted as *hot*. It is barely possible that MacWilliam in the stress of the experiment stopped to note the least perceptible difference in temperature from "warm" to "hot." It is, however, highly probable that he overshot the mark, 45 C., in his judgment of the sensation's quality. "Slight heating," then, as we interpret it, implies a temperature above 45 C., while "hot galvanocautery" may very well imply a temperature still higher, and therefore the temperatures used by MacWilliam may fall in our wider range, which make his findings agree with ours. The fact that results are obtained near the inferior cava in the rabbit is easily explained by the histologic picture as stated above.²⁰ With the qualifications, therefore, that the use of *proper* temperatures can produce impulse initiation in all of the sinus reuniens tissue, Erlanger's last sentence is true.

Somewhat the same kind of criticism could have been used in judging the results obtained by the temperature method on the cold-blooded heart, before we advanced data¹⁶ that seemed to explain the apparently contrary results. When Engelmann² localized the origin of the heart beat in the frog by the temperature method — using a

22. Erlanger: THE ARCHIVES INT. MED., 1913, 11, 334.

galvano thermo cautery—he found that he could transfer the pacemaker from one point to another by warming the latter. This transfer, indicated by an increased rate, occurred after a latent period. We,¹⁴ however, found that when a relatively low range of temperature was employed the rate could be influenced immediately and with no latent period at only one spot—the right sino-auricular junction—while with the use of a high range of temperature we could make the pacemaker appear after a latent period at various points on the sinus venosus and on the veins emptying into it. Such a shift of the pacemaker by proper thermic influence has been shown to occur in the sinus node itself¹¹ as well as from the sinus node to the a-v system. Also, in localizing the point of action of the vagi in the heart, cooling with various intensities yielded various results. These facts reveal the importance of proper interpretation. On the basis of work previously done on the cold-blooded hearts, we suggested that if any remnant of the sinus tissue in the normal warm-blooded heart be influenced so as to make it more automatic, it would either assume the pacemaking function or else it would in turn influence the primary pacemaker and thereby produce a change in heart activity. We found this to be the case as shown by our results. Other spots (I, IV, V, VIII) than the sinus node region were found, that, on being warmed, produced an increase in rate—a typical effect on cardiac activity.²⁰ This increase in automaticity, however, resulted when the high range of temperature was employed. With the low range only the sinus node was influenced. These results were produced by us repeatedly. Investigators in their search for a primary pacemaker warmed their thermodes up to 60 C. (the range being 40 to 60 C.). We found (Experiment E) that an increase in rate up to 22 per cent. could be produced at point IV with 56 C. We have obtained 2 to 10 per cent. increases at other points than the sinus node with temperatures close to 50 C., and for the purpose of finding a primary pacemaker even 50 C. is probably too high. A 10 to 20 per cent. increase in rate ought to be sufficient, and such increases are possible at temperatures even closer to body temperature. We have obtained such increases at 41 and 42 C. These results seem to indicate that in localizing the primary pacemaker with warm temperature the range should be a narrow one.

From results obtained by them in cooling and excising the sinus node, Brandenburg and Hoffman demand for all researches which are concerned with the significance of the sinus node as the point of origin of the normal cardiac impulses, that nondestructive methods be used, for only then will the results be clear and unequivocal. Previous to them Lewis²¹ commented on the fact that a “dislocation” of the pacemaker occurred with slight provocation.

Corroborative Data of Sinus Tissue Rhythmicity by Other Methods.—The fact that sinus tissue, exclusive of the S-A node, can display typical cardiac activity (rhythmicity) is substantiated by the following data obtained by other methods. It is a well known fact that in attempting to find the region of the dying heart which retains its power of contraction longest, investigators discovered sinus tissue (mouths of vena cavae, and coronary sinus) not only contracting but contracting rhythmically. These results were noted by inspection, by registration, and by the electronegative method (for references see Footnote 23). In Experiment D, after the S-A node had been destroyed by heat, we noted the assumption of rhythmicity in the termination of the superior vena cava. Apparently, of all the sinus tissue the S-A node is unique in not having been observed to have the property of contractility. Gunn and Chavasse²⁴ found in the vessels examined by them that epinephrin causes quiescent rings of the superior vena cava only to beat rhythmically and powerfully, and that the rhythmically contractile tissue is comprised in a region for at least 6 to 8 mm. from the veno-auricular junction. Cow²⁵ had previously stated that the pulmonary artery shows rhythmical contractility after epinephrin is applied to it. Macht,²⁶ however, makes no statement of the production of rhythmical contractions by epinephrin on the pulmonary artery either in his review of the literature, or in his own experiments. Cow's records, rather, show that their interpretation is incomplete unless emphasis be placed again on the difference between tonic contractility and rhythmical contractility as Wharton Jones did in 1852.²⁷ MacWilliam¹ noted acceleration of the auricle in the heart in situ by stimulation, while Erlanger and Blackman²⁸ obtained the same results when using auricular strips obtained from the sinus region. Erlanger,²⁹ whose work was confirmed by Moorhouse,³⁰ excised strips containing sinus reuniens tissue from the mammalian auricle (cat, rabbit, dog) and inferred from his experiments that all the strips possess approximately the *same grade* of rhythmicity. This fact seems to be disproved,¹⁷ nevertheless the fact remains that the sinus tissue is highly rhythmical. A coronary sinus rhythm has been demonstrated by Zahn¹⁰ by the temperature method, and by Eyster and Meek¹⁸ by the method of initial negativity. We believe that the potential significance of the sinus tissue exclusive of the S-A node has been brought

23. Eyster and Meek: *Heart*, 1914, 5, 137.

24. Gunn and Chavasse: *Proc. Roy. Soc. Med.*, 1912-1913, 86 B.

25. Cow: *Jour. Physiol.*, 1911, 13, 125.

26. Macht: *Jour. Pharmacol. and Exper. Therap.*, 1914, 6, 16.

27. Jones, Wharton: *Philosoph. Trans.*, 1852, p. 131.

28. Erlanger and Blackman: *Am. Jour. Physiol.*, 1907, 19, 125.

29. Erlanger: *Am. Jour. Physiol.*, 1910, 27, 87.

30. Moorhouse: *Am. Jour. Physiol.*, 1912, 30, 358.

out in the diverse experiments in which there has been an attempt to produce the first Stannius ligature in the mammalian heart by destruction or elimination of the node and tissue closely related to it. Success in all cases seems to depend on effectual removal of all the sinus tissue or the parts important for conduction, and probably therein lies the cause for the increase in rate noted in experiments even after complete excision of the S-A node. Coronary sinus rhythm had been theoretically postulated by Edens, Rihl, and Lewis.

Origin of the Impulse in the Specialized Tissue.—When the temperature method is used, there seems to be some question as to whether or not the impulse arises at a narrow, definite point, or whether it is the resultant of the metabolic influences at play in all the sinus reunions tissue, or all the sinus node. In a part or in all of this sinus musculature the heart rhythm is believed to be initiated.¹⁰

Ganter and Zahn⁴ comment that the assumption of impulse initiation by a spot in the sinus node other than the head end *after warming* increases its automaticity is a reasonable view to take, but not quite so reasonable a view can be taken after cooling the same spot. They say that it is difficult to understand how a less automatic spot whose automaticity is further decreased by cooling can assume the pacemaking function. They explain the results by saying that normally every part of the sinus node contributes its definite share in the formation of an impulse, and therefore for each impulse a definite amount of energy is required and produced by the entire sinus node. Heat will develop this amount quicker, and cold contrariwise. They recognized the fact that Engelmann produced a shift of the pacemaker. The electronegative method, however, has shown that the pacemaker can shift even within the sino-auricular node itself.¹¹ If the electric potential which thus shifts is the sum of influences in the sinus tissue, as Ganter and Zahn claim, then it seems strange that *the heating* which is then merely heating the electric potential at that point should in turn change the activity of the entire tissue itself.

To What Extent Can Nerve Influences Be Excluded.—That there is an abundant supply of ganglia and nerve-fibers to the S-A node and the sinus tissue is well known (Meyer, Gaskell, Dogiel, Engelmann, Jolmann, Bethe, Carlson, Langley, Langendorff, Keith and Flack, Flack, Koch, Mönckenberg, Keith and Mackenzie, Mackenzie, Morison, Argand, Eyster and Meek, Meikeljohn, de Witt, Lewis, Oppenheimer and Oppenheimer, and others). This is true for the cold-blooded heart as well as the mammalian heart. With particular reference to the latter this much can be stated, that an appreciable portion of this ganglion and nerve-fiber supply is continuous with the vagi, sympathetics, and possibly depressor. Further, that these in turn — especially the chrono-

tropic fibers of the vagus and sympathetic — are in close relation to the S-A node (Flack, Rothberger and Winterberg, Ganter and Zahn, Marchand and Meyer, Cohn, Eyster and Meek, and Schlomovitz, Eyster and Meek). Another portion of the ganglion and nerve-fiber supply may be outlying stations ultimately connected with the nerves mentioned above, or with the S-A node, or both. If so, this would allow the possibility of local reflexes. Our conception of this distribution is naturally limited to the nerves named and the S-A node, since up to the present they only are recognized as entities, both anatomically and physiologically. In lieu of the above facts the location of the main paths of the inhibitory and accelerator cardiac nerves must be considered in relation to the influence especially of large temperature variations, as temperature alteration of such paths might influence the pacemaker indirectly. It is probably proved that atropin effectively rules out vagal activity on the heart. MacWilliam says that the response of the hearts to heating was the same in atropinized and unatropinized animals. Eyster and Meek report no differences in regard to the behavior of the pacemaker in atropinized and unatropinized animals. With the vagi intact it is possible to increase their efficiency by warming them and so cause a slowing of the heart, but the latter has not been confirmed by the experiments of MacWilliam, Adam, Ganter and Zahn, Zahn, and Brandenburg and Hoffman. In our experiments, out of a total of 412 readings there were 210 in which the high temperature range was used, and in eight of the latter, or 4 per cent., there was a decrease in rate of 3 to 11 per cent. (average 6 per cent.). The eight occurred in Experiments A, B, C, and F, while of the eight there were four in F alone. On the other hand, warming may increase the efficiency of the accelerator fibers and cause an increased rate either when there is simultaneous warming (a) of the vagi, or (b) of sinus tissue, or (c) of both, so that the automaticity of the sinus tissue is gradually increased until it becomes the pacemaker. Either (b) or (c) seem to be the explanation of our data where results were obtained only after a long latent period. The influence of the accelerators cannot be removed as easily as that of the vagi. We must wait for a drug as efficient as atropin without doing damage to the tissues, or else carry out a series of experiments with the accelerator mechanism effectively excluded (excision, etc.). The use of ammonia (Fredericq), cocain, nicotin, apocodein, etc., is discountenanced by Brandenburg and Hoffman, and by all those who consider the automatic tissues to constitute a delicate mechanism. In our present state of knowledge the accelerator mechanism in the cardiac tissue itself cannot be eliminated. This statement applies as well to the local reflex mechanisms that probably exist in the heart but have not yet been shown to be functional units. In addition to these

facts, it is difficult to administer a drug which we are certain has little effect on the S-A node or sinus tissue when used on nerve elements, or vice versa. In our experiments nerve influences were minimized by ether anesthesia, but not sufficient to make radical elimination. Therefore, we submit these facts as a basis for further research.

SUMMARY

Effect of Thermic Stimulation of Sinus Reunions Tissue as Determined by the Methods Described.—

1. Thermic stimuli, with a temperature range above and close to that of the body, in the warm-blooded animal, will produce an increase in rate only when placed on the sino-auricular node. These are stimuli in a narrow temperature range, and at lower temperatures than heretofore employed.

2. Thermic stimuli considerably above body temperature will produce an increase in rate when applied on any of the sinus musculature in the mammalian heart. These are stimuli in a wider range. These results have also been obtained at the same temperatures used by other investigators in localizing the sinus node as the seat of impulse initiation and the only sinus tissue revealing typical cardiac activity.

3. It is important to note for how long a time thermic stimuli are applied.

4. Sinus tissue other than the S-A node when properly influenced by thermic stimuli will display the power of impulse initiation.

5. The response of a certain region may be the result of increase of its automaticity by the heat until it becomes the pacemaker, and does not necessarily mean that it was the seat of impulse initiation before the heat was applied.

We are glad to express our indebtedness to Professors Carlson, Eyster and Meek, of the Universities of Chicago and Wisconsin, respectively, for suggestions and assistance.

PYOPNEUMOTHORAX AND PNEUMOTHORAX

A REPORT OF TWO CASES WITH INTERESTING CLINICAL
AND ROENTGENOLOGIC FINDINGS *

JAMES A. HONEIJ, M.D.

NEW HAVEN, CONN.

Pneumothorax alone, or accompanied by serous fluid, or by pus, is infrequent enough in any single clinic to be of sufficient interest to study and report. In the present case of pyopneumothorax (Case 1) there is added interest on account of the obscured physical signs and symptoms, the unusual partial encapsulation of the pneumothorax, as shown by roentgenogram, and the transmitted cardiac pulsation through the fluid.

In the majority of cases the collapsed lung is easily discernible by Roentgen ray and can be made out by percussion near the mediastinal border, in contrast to the hyperresonant, tympanitic condition of the rest of the chest, and at the base of the pleural cavity the fluid can be easily marked out. In a typical case of pneumothorax, such as is reported here, and which preceded the present case of pyopneumothorax by a few weeks, diagnosis is not a difficult matter. When atypical complicated cases present themselves, diagnosis is increasingly difficult.

The normal pleura is not visible by roentgenography. When, however, pathologic changes occur, and there is thickening of the pleura, or when definite bands of adhesions result, then such changes are capable of being diagnosed by roentgenographic methods.

If there is serous fluid in the pleural cavity sufficient to give physical signs or symptoms, and if there is with it a pneumothorax condition, then the roentgenoscopic examination will determine it.

In partial pneumothorax conditions, pleural adhesions may, to a certain degree, limit the extent of both the air and fluid in the cavity. If the adhesions are along the median line, the displacement of the heart by the fluid and air is restricted; in cases in which the adhesions occur between diaphragm—especially in its central and dome portion—and pleura or mediastinum, a true comparison of the position of the diaphragm is impossible, and when adhesions extending transversely across the pleural cavity occur—especially in the upper one-third of the chest—the true extent of the pneumothorax and the position and the outline of the diseased lung cannot be determined. Likewise, is it impossible to determine the existence of tuberculosis

* Submitted for publication April 23, 1917.

in the upper lobe of the lung—if not collapsed—or in any part of the atelectatic lung.

The presence of large amounts of fluid adds to the difficulty of diagnosis, as a diagnosis of fluid in the pleural cavity, as such, is of little value unless the associated condition of the chest contents and their function can be given.

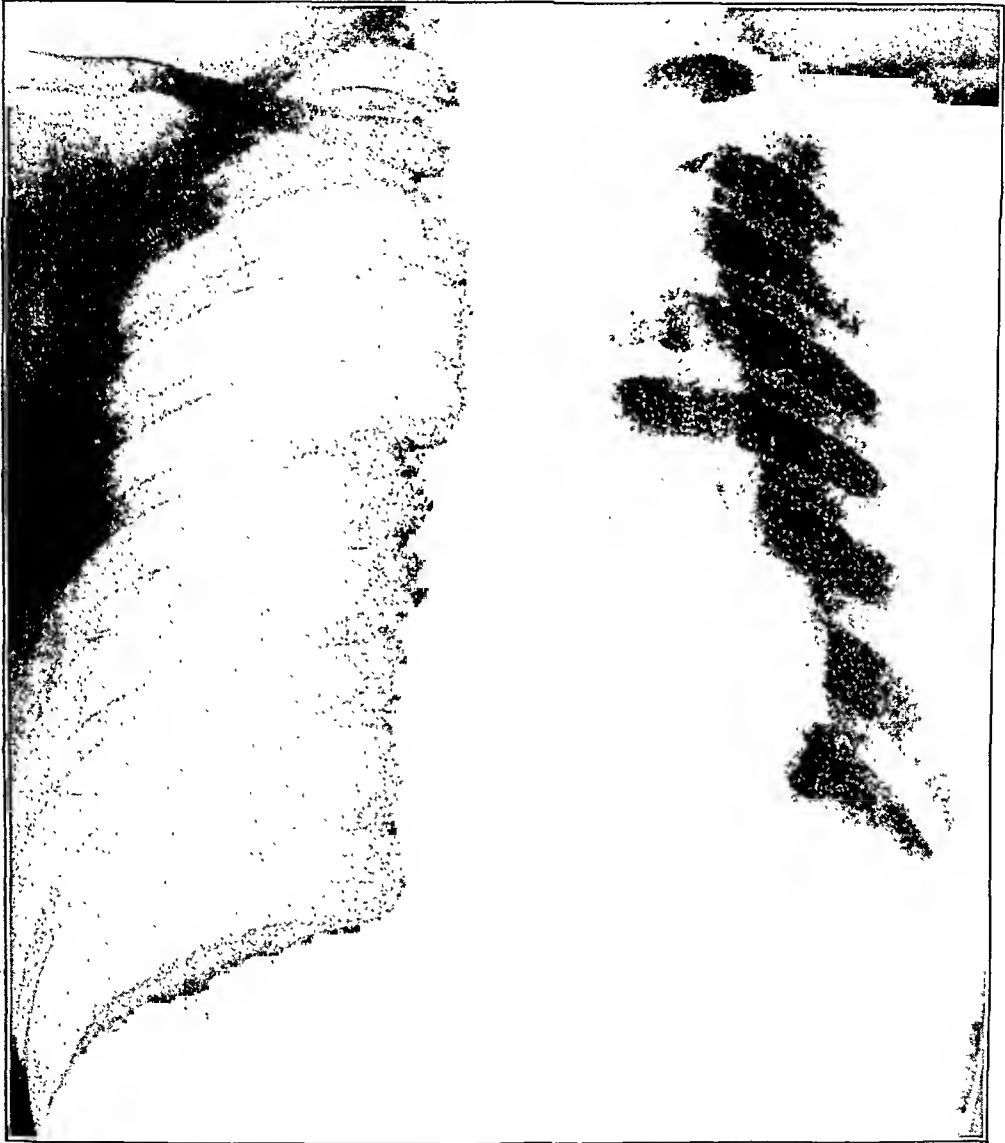


Fig. 1.—Case 1 (Hosp. No. 214). Pneumothorax of left chest; diaphragm at twelfth rib; collapsed lung visible between seventh and tenth ribs, near mediastinum; heart displaced to right.

In probably no other condition of the chest is the value of combined clinical and roentgenographic methods so well illustrated as in the pneumothorax, hydrothorax or pyopneumothorax cases. In Case 1, of pyopneumothorax, this is well brought out.

REPORT OF CASES

CASE 1.—(Hosp. No. 214.) *Pneumothorax*.

History.—March 8, 1917. Woman, aged 27, with a history of a slight attack of vomiting on March 3; no history of pain in the chest; patient has lost 15 pounds in the previous six weeks.

Physical Examination.—The patient is of fairly normal build and development. Physical examination shows a slight bulging of the left chest, with intercostal spaces flush with the ribs; the percussion note is higher pitched on the left and is tympanitic; respiration is faint, and amphoric breathing is heard over the entire left side; definite coin sound elicited. The heart is displaced to the right 10 cm. from the median line.

The roentgenograms show a marked contrast between the right and left lung. The right lung is dense—apparently compressed—as evidenced by the increased shadows at the hilus. Throughout the lung, and especially at the apex, definite mottling is seen. The left chest is transparent—a pneumothorax condition—and near the hilus is the more or less butterfly-wing outline of the atelectatic lung.

The heart and mediastinal vessels are displaced to the right to a considerable extent. The diaphragm on the left is lower than normal; the diaphragm on the right is higher than normal.

Diagnosis.—Pneumothorax, atelectasis. Probable pulmonary tuberculosis. Displaced heart.

March 9, patient aspirated and percussion of the heart shows it to be 7 cm. to the right of the median line; physical signs the same.

Roentgenograms show the heart slightly less displaced by approximately 1 cm. The collapsed lung is denser and the remaining left chest space is slightly less transparent. The costocartilaginous articulations show marked calcification.

On discharge (March 12) breath sounds over left lung still diminished and coin sound distinct; apex beat neither visible nor palpable.

CASE 2.—(Hosp. No. 291.) *Hydropneumothorax*.

History.—March 29, 1917. Man, aged 51, with history of shortness of breath for five weeks, which has been more marked in the previous three weeks; pain in left chest.

Physical Examination.—The patient is of normal build and fair development, but emaciated. Physical examination shows both apices to be sunken, clavicles prominent; dulness of right apex to the second rib; breathing is harsh and a few râles are heard at the right apex after coughing; tactile fremitus in right axilla; Grocco's sign on the right side; on the left there is dulness from the ninth dorsal spine downward, which is modified when the patient lies on his right side. There is visible and palpable pulsation of the chest in the left post axillary line from the middle of the scapula down to the base; heart displaced to the right.

Diagnosis.—The clinical diagnosis suggested possibly an aneurysm, pericardial effusion and pulmonary tuberculosis.

The patient was partially delirious and difficult to control; was unable to lie down, and suffered with frequent paroxysms of pain in the lower left chest, making the examination difficult both from a clinical and roentgenographic point of view.

The roentgenograms show the heart much displaced to the right. The displacement arises at the first rib and extends gradually and obliquely downward to the right base. The right heart outline is distinctly seen converging at right angles to the diaphragm. The lung on the right is not clear, although it is emphysematous and the diaphragm is very low. The left lung shows marked density and mottling at the apex and to the first space, where it is definitely demarcated by a dense semicircular line 1 cm. wide, which arises from the hilus region and extends upward and outward to the axilla. Below this curved

line there is a large, clear transparent area, more or less oval in outline, extending to the fifth rib. From the fifth rib downward great density occurs. The diaphragm is not discernible. Barium sulphate in emulsion was given the patient to determine the position of the fundus of the stomach; the roentgenograms show this organ to be situated low in the pelvis, and consequently bears no relation to the process above.

Fluoroscopic examination indicates the surface line of the fluid at the base to be more horizontal than appears on the roentgenograms, and with inspiration there is a slight movement of this line.

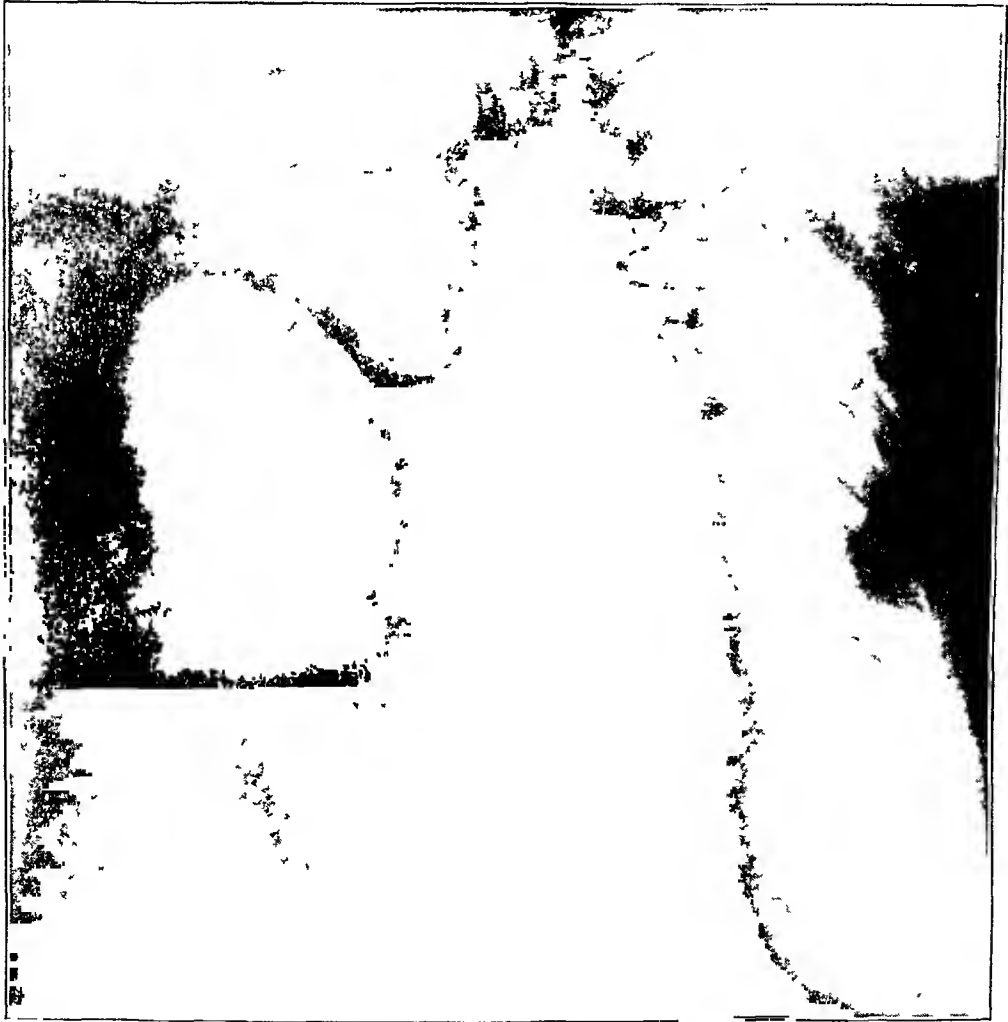


Fig. 2—Case 2 (Hosp. No. 291). Hydropneumothorax. Patient erect; shows line of fluid on left at ninth space; band of adhesions seen transversely across upper part of chest from seventh rib near mediastinum to middle of scapula on the outer side; compensatory emphysema on the right; diaphragm at eleventh space; heart displaced to right.

Displacement of the heart to the right as shown in this case, without greater symptoms and physical signs, does not suggest aneurysm. The heart outline on the right, especially at its juncture with the diaphragm, suggests some fluid in the pericardium. The density at the left apex and the zone of transparency below this indicates a pneumothorax—atelectasis of the lower lobe—with fibrous

adhesions encapsulating the pneumothorax area. The greater density at the base is probably fluid.

The pulsation cannot be explained in any other way than that it is transmitted through the fluid to the outer chest wall from the heart. Were the pulsation present in the upper axilla only, it might be explained by the fibrous adhesions and compressed lung.

April 3. Clinical examination elicits a shifting dulness at the base when the patient shifts his vertical position to the semiprone or horizontal. Above this area a definite coin sound is now obtained; succussion is heard. The roentgenographic diagnosis is verified.



Fig. 3.—Case 2 (Hosp. No. 291). Hydropneumothorax. Patient prone, shows fluid throughout left chest to the curved band of adhesions. For comparison with Figure 2.

April 5. The patient is aspirated and approximately 11 ounces of foul-smelling pus removed.

April 6. Repeated roentgenographic examination shows the following changes: The density of the left base extends perhaps a little higher, and the density of the upper left lung and the whole of the right show a more detailed mottling than previously seen. With the patient in the prone position the roentgenogram shows that the density seen previously at the left base has extended upward and is now apparent throughout the whole of the left chest,

even extending beyond the curved zone previously described. This definitely proves the presence of free fluid in the left pleural cavity.

April 7. Resection of ribs. Operative findings: Pleural cavity contains about 1,000 c.c. of very foul, moderately thick pus. The upper lobe of the left lung, as far as could be felt, collapsed, but apparently normal. The lower lobe of the left lung is partially destroyed, the remaining portion being very much infiltrated. The heart is displaced beyond the vertebral column to the right; pericardium much thickened and contains a moderate amount of clear fluid; heart about normal, in size, and there is a dense adhesion between the apex and pericardial side. The patient died on this date.

It is of interest to note that an almost identical case of hydropneumothorax is reported by Aimé,¹ occurring in a French soldier infected with pulmonary tuberculosis. The pleural cavity was divided by a fibrous band extending from the diaphragm upward to the compressed lung, forming an outer and an inner air pocket; also dividing the fluid at the base of the lung into two portions. The diagram and roentgenogram are reproduced here.

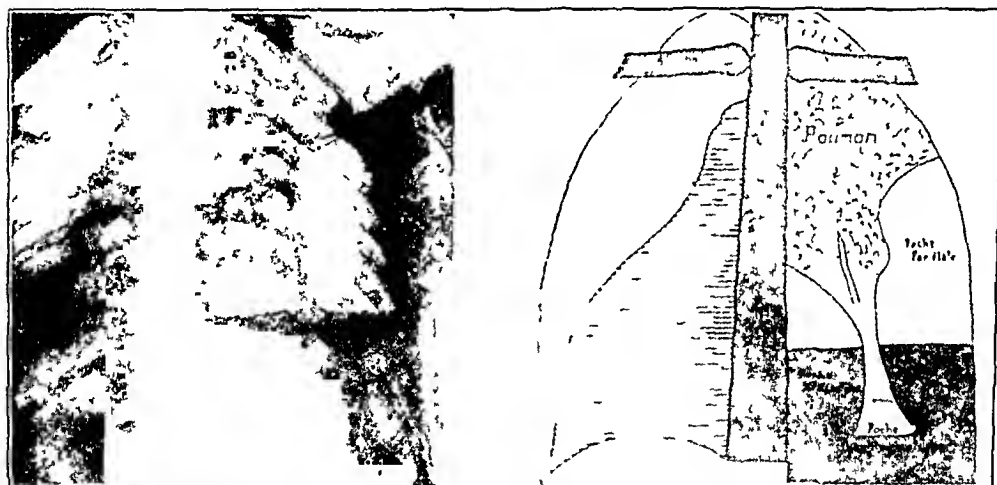


Fig. 4.—On the left, roentgenogram of Aimé's case of right hydropneumothorax with pockets. At the right is a tracing of the figure on the left.

In respect to the pulsation described in Case 2 (Hosp. No. 291), a very interesting article is reported by W. P. Herringham.² Among other cases he reports one of pulsating hemopneumothorax in a soldier, as follows:

Hit July 29, 1916, by a bullet on the outside of left shoulder. Hemoptysis followed.

July 30. Heart's apex impalpable; right border a little displaced to the right (by percussion and auscultation). Lungs: right, front, natural; left, front, surgical emphysema obscured everything.

1. Aimé, P.: Right Hydropneumothorax with Several Pockets in a Tuberculous Individual, *Jour. de radiol. et d'électrol.*, 1916, **2**, 323; abstr., *Am. Jour. Roentgenol.*, 1917, **4**, 199.

2. Herringham, W. P.: On the Early Stage of Wounds of the Chest, *Quart. Jour. Med.*, 1916-1917, **10**, 79.

August 5. On the left side an impulse thought to be due to the cardiac apex was felt in the fifth space. The usual cardiac dullness seemed to be present. It was continuous with the impairment of the left side and back. The upper front was tympanitic. There was no breath sound; no bell sound. Pulsation was palpable up to the clavicle.

August 6. The left side was bulging still and there was a slight local prominence under the clavicle. Pulsation as on August 5, but the heart was obviously beating on the right side as far out as the nipple line. The impulse felt in the left fifth space both August 5 and 6 could not therefore be cardiac. It was the same as the impulse felt in the upper resonant area. An occasional tinkling sound was heard.

August 8. Same signs; well-marked succussion splash both heard and felt; general condition excellent; no distress; temperature normal. Evacuated to base.

The author then concludes by stating that "Pulsating empyema is known, but I have never heard of pulsation in a pleura containing air and blood. When the pulsation was first noticed my colleagues in the clearing station and I held long consultations over the case. We could think of no known condition likely to produce it except aneurysm. But the impulse was not like that of an aneurysm; there was no bruit and an aneurysm of that size must have produced distress. In the absence of any constitutional symptoms pyopneumothorax can be excluded."

From a diagnostic and physical point of view it is obviously of little importance what the medium is through which pulsation takes place, as long as it is fluid. Certainly from the roentgenologist's standpoint it is important.

In both these cases fairly definite signs of pulmonary tuberculosis were present, and, as is well known, tuberculosis is the primary cause of this interesting condition in the majority of cases.

I am indebted to Dr. George Blumer and Dr. Wilder Tileston for these cases, on whose services they occurred.

ASTHMA COMPLICATING THE SERUM TREATMENT OF PNEUMONIA *

H. L. ALEXANDER, M.D.
BOSTON

As the use of antipneumococcus horse serum becomes more extensive, cases are met with wherein sensitiveness to serum complicates its administration, as happens with the therapeutic use of other serums. The reaction induced by giving horse serum to such patients may vary, depending on several factors, among which is liability to "horse asthma." Patients with this condition complain that proximity to horses, whether currying them, driving them, or even going into stables, may bring on symptoms which are typical of bronchial asthma, due doubtless to suspended particles of horse dandruff or horsehair. Walker¹ has found that most patients suffering from this condition give positive cutaneous reactions to horsehair proteins, whereas in addition a much smaller number (22 per cent.) react to horse serum proteins. Woodehouse² has established the fact that the fractional portions of the protein mixture hair, may sensitize, or rather, that its administration results in multisensitization to its individual proteins. Similar reactions have been demonstrated in plant proteins by Lake, Wells and Osborne,³ and others. On the other hand, it is questionable whether any one protein of hair is identical with any protein of serum, although it will be shown that a close relationship exists.

At the Peter Bent Brigham Hospital where, during the past winter, antipneumococcus serum was administered to fifteen patients with Type I⁴ infection, three cases were encountered in each of which there was a definite history of "horse asthma." This is a higher incidence than has been met with either at the Hospital of the Rockefeller Institute, from which we obtained our serum through the courtesy of Dr. Cole, or at the Presbyterian Hospital, New York, where serum has been used extensively. It is appreciated that so small a number of cases as here reported forbids conclusive deductions, and the value attributed to the cases lies rather in their constant manifestations and

* Submitted for publication July 12, 1917.

* From the Medical Service of the Peter Bent Brigham Hospital.

1. Walker, I. C.: *Jour. Med. Research*, 1917, **35**, 497.

2. Woodehouse, R. P.: *Jour. Immunol.*, 1917, **2**, 237.

3. Lake, G. C.; Wells, H. G., and Osborne, T. B.: *Jour. Infect. Dis.*, 1914, **14**, 364, 377; 1915, **17**, 259.

4. Cole, Rufus: *Treatment of Pneumonia by Means of Specific Serums*, *Jour. Am. Med. Assn.*, 1913, **61**, 663.

in the experience gained in giving considerable quantities of serum to such patients. Antipneumococcus serum is used in large doses, 90 c.c. or more, intravenously, which far exceeds the amounts ordinarily used of other serums.

A cutaneous test, similar to the von Pirquet test, with whole dried serum protein with the addition of a little tenth-normal sodium hydroxid to dissolve it, was made on all patients before treatment. Of the three asthmatic patients, but one reacted positively. A cutaneous test with horsehair protein was also made on this patient before treatment and was found to be positive, whereas it was made after treatment in the other two, and was likewise positive in each. Treatment with serum did not induce a positive cutaneous reaction to horsehair in several of the nonasthmatic individuals tested at varying intervals, and so it may be assumed that all these asthmatic patients would have given a positive skin reaction to horsehair if tested before treatment with antipneumococcus horse serum. On the other hand, the history of asthma was definite enough in each instance to demand caution in administering serum. It was not determined whether the intracutaneous test, far more sensitive than the cutaneous, made with serum would be positive in the cases reacting to horsehair.

REPORT OF CASES

CASE 1.—J. C., a man aged 25, formerly a teamster, gave a family history of asthma in that his father and two brothers suffer with it. The patient has had attacks of asthma off and on for fifteen years. He could drive horses but could not groom them. The onset of the present illness dated four days before admission with a chill, pain in the right chest, cough and fever, which persisted. He was admitted Jan. 11, 1917, with a temperature of 103.8 and signs of consolidation in the right upper lobe. Type I pneumococcus was isolated from his sputum. The cutaneous test with horse serum protein was negative. One c.c. of horse serum was given subcutaneously one hour before treatment, without reaction. Anti-pneumococcus Serum I diluted with equal parts of physiologic sodium chlorid solution was allowed to run slowly into a vein of the arm. When about 70 c.c. of serum (140 c.c. of the mixture) had been injected, the patient's face suffused quickly, his eyes watered, respirations began to be labored and rapid, and he complained of a sense of tightness in his chest. The infusion was discontinued at once. Auscultation revealed loud asthmatic breathing. A typical attack of bronchial asthma soon developed, lasting about one-half hour, which was partially controlled by epinephrin. No further symptoms developed. His temperature fell to normal and further treatment with serum was not necessary.

January 26: Cutaneous tests were made with the proteins of doghair, cat-hair, rag weed, golden rod, corn, grass, poplar leaves, maple leaves, *Staphylococcus albus*, *Staphylococcus aureus*, and *Bacillus diphtheroidae*, all of which were negative. Red top was positive, horsehair was positive. The component proteins of hair gave negative reactions with alkali-metaprotein, and coagulated protein, whereas peptone was positive in dilutions of 1:100 and 1:1,000.

CASE 2.—H. B., aged 42, formerly a fireman, had been subject to asthma for fifteen years. This was induced by horses and hay dust in the fire house and aggravated by smoke. He was admitted Feb. 6, 1917. His present illness

began three days before with a chill, fever and cough. On admission his temperature was 104; no pathologic signs were found in the lungs on physical examination but a roentgenogram revealed a central consolidation of the left lower lobe. Type I pneumococcus was isolated from his sputum. Cutaneous tests with horse serum and horsehair proteins were strongly positive.

In an attempt to desensitize to horse serum, the procedure was as follows:

February 7, 2:20 p. m., 0.25 c.c. antipneumococcus serum subcutaneously; violent asthma in fifteen minutes, lasting twenty minutes.

3:30 p. m., 0.025 c.c. antipneumococcus serum subcutaneously. No reaction.

4:15 p. m., 0.066 c.c. antipneumococcus serum subcutaneously. No reaction.

4:45 p. m., 0.1 c.c. antipneumococcus serum subcutaneously. No reaction.

5:15 p. m., 0.25 c.c. antipneumococcus serum subcutaneously. No reaction.

5:30 p. m., 0.5 c.c. antipneumococcus serum subcutaneously. No reaction.

6:00 p. m., 1 c.c. antipneumococcus serum subcutaneously. Urticaria over entire body.

8:00 p. m., 2 c.c. antipneumococcus serum subcutaneously. Urticaria fading.

8:30 p. m., 1 c.c. antipneumococcus serum intravenously. Nausea, vomiting, violent asthma in ten minutes.

10:00 p. m., 1 c.c. antipneumococcus serum intravenously. Nausea, vomiting; no asthma.

11:10 p. m., 2 c.c. antipneumococcus serum intravenously. No reaction.

12:00 m., 4 c.c. antipneumococcus serum intravenously. No reaction.

February 8, 12:45 a. m. Antipneumococcus Serum I with equal parts of saline was allowed to run slowly into a vein. After 70 c.c. of serum (140 c.c. of the mixture) had been given, the face became suffused, eyes watered, and patient complained of "itching all over." Infusion was discontinued. Within ten minutes there were nausea and vomiting but no asthma developed.

12:00 m. Temperature 99. Cutaneous tests with horse serum and with horsehair protein were negative.

8:00 p. m. Temperature 101.4. One c.c. of antipneumococcus serum was given intravenously. There was no reaction.

9:15 p. m. Antipneumococcus serum and saline were infused slowly. When 65 c.c. of the serum had run in, the face became suffused, and eyes began to water; treatment was stopped. In ten minutes an asthmatic attack began lasting fifteen minutes. There was no further reaction.

February 9. Temperature 99. Cutaneous test with horsehair protein negative. Horse serum protein negative.

February 13. Cutaneous test with horsehair protein slightly positive. Horse serum protein negative.

February 16. Cutaneous test with horsehair protein moderately positive. Horse serum protein negative.

February 20. Cutaneous test with horsehair protein moderately positive. Horse serum protein negative.

February 23. Cutaneous test with horsehair protein moderately positive. Horse serum protein negative. Proteins of timothy and red top negative.

February 26. Cutaneous test with horsehair protein strongly positive. Horse serum protein negative.

February 28. Cutaneous test with horsehair protein moderately positive. Horse serum protein negative. Cutaneous test with horsehair alkali-metaprotein, 1:100, positive; 1:1,000, positive; 1:10,000, negative.

May 1. Cutaneous tests with horsehair alkali-metaprotein and peptone were positive in dilutions to 1:1,000. Those with whole horse serum protein, serum albumin, euglobulin, and pseudoglobulin, were all negative. The patient has been working as a chauffeur and gasoline vapor causes a little difficulty in breathing, but there has been no typical asthma.

CASE 3.—H. R., aged 37, was fond of horses and did considerable driving about ten years ago, but was compelled to give this up because it caused water-

ing of the eyes, sneezing and some difficulty in breathing. He had not been similarly affected since. The present illness began four days before serum treatment with a chill, pain in the right chest, and fever. May 6, 1917, signs of consolidation were found over the entire right lung. May 7, pneumococcus, Type I, was isolated from the sputum. Temperature 103; patient was very ill. Cutaneous test to horse serum, negative; 0.25 c.c., 0.5 c.c. and 1 c.c. of serum were given subcutaneously, then 0.5 c.c. and 1 c.c. intravenously, at fifteen minute intervals, but no reaction whatever was noted. Intravenous infusion with serum diluted with saline was begun. When about 40 c.c. of serum had been administered, the patient's face rapidly flushed, and treatment was stopped. In a few minutes he became restless and had an asthmatic attack which persisted for one-half hour. Eight hours later serum was again infused without attempted desensitization. After 40 c.c. had run in, a reaction similar to that after the first treatment occurred. Six and a half hours later, serum was given, and 60 c.c. were tolerated before a mild reaction occurred. Another injection eight and one-half hours later brought on a mild reaction after 65 c.c. of serum had been given. A fifth infusion was administered after six hours, and 75 c.c. of serum were tolerated before a mild reaction occurred. In six hours another serum treatment was given, and 70 c.c. injected when a moderate reaction appeared. The patient was extremely ill, and the pneumonic process had extended into the left lower lobe. He rallied after the last infusion and became progressively better thereafter. A cutaneous test with horsehair protein on June 16 gave a strongly positive reaction; that with horse serum was negative.

COMMENT

From these cases it is apparent that there is a distinct difference in the reaction to horse serum infusion, depending on whether the individual is sensitized to hair, or to both serum and hair. In the first instance, desensitization with small amounts of serum seems to be of no avail, as it requires a considerable quantity, 40 c.c. or more, to produce a reaction. In that most patients with "horse asthma" may be easily desensitized with small amounts of horsehair protein,⁵ it is quite likely that such desensitization would have averted the reactions induced by large amounts of serum. In all the cases, the cutaneous test to horsehair persisted long after treatment, excepting the immediate desensitization, which was but transient, in Case 2. On the other hand, the reaction to horse serum protein was in no instance positive after treatment.

In none of these cases were there evidences of serum sickness, excepting a few doubtful changes in Case 3. This patient had moderate soreness of his temperomaxillary joints for one day and a little difficulty in breathing twelve days after the last serum injection. This contrasts sharply with the nonasthmatics in whom manifest serum sickness of more or less severity occurred in almost every case.

The reaction brought about only by large amounts of horse serum has not been studied. Obviously, it is anaphylactic. Wells and Osborne⁶ maintain that the specificity of the anaphylaxis reaction is

5. Walker, I. C.: Jour. Med. Research, 1917, **36**, 243.

6. Wells, H. G., and Osborne, T. B.: Jour. Infect. Dis., 1913, **12**, 341.

determined by the chemical structure of the reacting proteins rather than by their biologic origin, and that the entire protein molecule is not involved in the specific character of the reaction, but this is developed by certain structural groups contained therein. Consequently, it is possible that such a group of one of the proteins of the serum may be identical with a group of the hair, to which the patient is sensitized, and as serum is introduced, the action of this group remains subliminal until a quantity, usually large, has been administered, sufficient to cause symptoms. Another explanation is in accordance with the work of Manwaring and Kusama.⁷ They perfused the lungs of guinea-pigs which had been immunized by frequent injections of goat serum with the blood of these guinea-pigs and goat serum, and thereby demonstrated a coincident fixed cellular hypersensitiveness and humeral immunity. Dale⁸ had previously demonstrated the occurrence of cellular hypersensitiveness. It is conceivable that in the above patients such an excess of serum was given that their blood no longer protected, and hypersensitiveness of the tissues became manifest.

SUMMARY

Pneumonia patients with "horse asthma" reacted differently to infusions of antipneumococcus serum, depending on whether they were sensitive to horsehair and horse serum, or to horsehair alone. In the first instance, not even small subcutaneous injections of serum could be tolerated, whereas in the latter, no reaction occurred until considerable quantities of serum had been given, although the cutaneous test with serum had been negative. This suggests a close relationship between one or more of the horse serum proteins and those of horsehair.

Patients sensitive either to serum or hair could be desensitized so that eventually doses of serum sufficient to produce a curative effect on the pneumonic process were given. Therefore, asthma apparently does not contraindicate the employment of antipneumococcus serum.

There were few or no manifestations of serum sickness in asthmatic patients, even after as much as 350 c.c. of antipneumococcus horse serum had been infused, whereas in nonasthmatic patients, serum sickness almost always occurred.

7. Manwaring, W. H., and Kusama, Y.: *Jour. Immunol.*, 1917, **2**, 157.

8. Dale, H.: *Jour. Pharm. and Exper. Therap.*, 1912, **4**, 167.

The Archives of Internal Medicine

Vol. XX

NOVEMBER, 1917

No. 5

THE RENAL FUNCTION IN GOUT *

C. W. McCLURE, M.D.
BOSTON

That gouty subjects are prone to nephritis has long been recognized. Nevertheless, patients coming to necropsy and in whom uratic deposits are found in the toe joints may show signs of nephritis so meager as to be ascertainable only by microscopic examination of the kidneys.¹ Frequently clinical examination of gouty patients fails to elicit symptoms which permit the diagnosis of chronic nephritis. Because of this the great majority of observers have interpreted the findings of metabolism experiments in gout on the supposition that the functional condition of the kidneys was normal. Since their results were obtained by the study of substances excreted into the urine the importance of knowing the degree of renal function is apparent. Only within a comparatively few years have methods been developed which give trustworthy information concerning efficiency of the kidneys. Using these methods, I have made a study of renal function in gouty patients with tophi. In these the diagnosis of chronic nephritis was either not made or its presence was questionable. The cases are comparable to those reported in the literature on which previous observers have carried out the metabolism studies.

The maximum normal limit of the amount of nonprotein nitrogen in the blood is considered at 35 mg. per 100 c.c., and for urea nitrogen 20 mg. per 100 c.c.² The minimum normal of the McLean index³ of urea excretion is 80 per cent. The normal excretion of phenolsulphonephthalein in two hours ranges between 60 per cent. and 80 per cent. In the two hour renal test⁴ specimens of urine were collected every two hours from 7 a. m. to 9 p. m., and one night specimen from

* Submitted for publication May 15, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Garrod, A. E.: *The Chemical Pathology of Gout*, Brit. Med. Jour., 1904, 2, 741.

2. McLean, F. C., and Selling, L.: *Urea and Total Nonprotein Nitrogen in Normal Human Blood. Relation of Their Concentration to Rate of Elimination*. Jour. Biol. Chem., 1914, 19, 31.

3. McLean, F. C.: *The Numerical Laws Governing the Rate of Excretion of Urea and Chlorids in Man*, Jour. Exper. Med., 1915, 22, 212.

4. O'Hare, J. P.: *A Study of Salt, Nitrogen and Water Excretion in Nephritis*, THE ARCHIVES INT. MED., 1916, 17, 711.

9 p. m. to 7 a. m. In each specimen the volume, specific gravity, total nitrogen, percentage concentration of nitrogen, total salt and the percentage concentration of salt were determined. In the urine of persons with normal kidneys there is considerable variation in each of the above named elements in the different two-hourly specimens. Renal functional changes are indicated by a fixation and lowering of one or several of the elements measured. More than 400 c.c. of urine voided between the hours of 9 p. m. and 7 a. m. is considered an abnormal increase in the night amount. The findings in the two-hour renal test have been interpreted by Dr. James P. O'Hare. To these standard tests one has been added in which the effect of ingesting sweetbreads on the nonprotein nitrogen of the blood is determined. This will be discussed later. For purposes of comparison the first two protocols represent the findings in two patients without gout. In the first case the effect of the ingestion of sweetbreads on the nonprotein nitrogen of the blood and on the excretion of uric acid is given. Detailed studies of the exogenous uric acid excretion in the four succeeding cases have been made and will be reported by Pratt and myself.

TECHNIC

Uric acid in the blood was determined by the methods outlined by Folin.⁵ On the advice of Folin the "uric acid reagent" was used instead of the "uric acid-phenol reagent" in quantitating uric acid in the urine. Urea was determined by the urease method of Van Slyke and Cullen.⁶ The total nonprotein nitrogen of the blood was estimated by the direct Nesslerization method of Folin and Denis.⁷ Nitrogen of the urine was determined by the Kjeldahl method. Chlorids were quantitated by Goodall's modification of Volhard's method.⁸

The results of the renal function studies are given in the following protocols.

PROTOCOLS

CASE 1.—R. L. Medical No. 5523. White, man, aged 35.

Diagnosis: Cirrhosis of the liver.

The patient drank large quantities of alcoholic beverages. He had undergone abdominal paracentesis for the removal of ascitic fluid twice in the previous year. His condition at the time of the metabolism experiment was good. Physical examination was essentially negative. There were no evidences of cardiovascular disease. Blood pressure was 130 mm. systolic and 70 mm. diastolic. The liver edge was palpable 3 cm. below the right costal margin.

Clinical pathologic findings in the urine: Nov. 12, 21, and Dec. 12, 1916. Urine amber, clear, acid, specific gravity 1.012 and 1.019, no trace of albumin with the heat and acetic acid test; a rare hyaline or granular cast; no erythrocytes, no pus cells, no epithelium.

5. Folin, O.: *Laboratory Manual of Biological Chemistry*, New York, 1916.

6. Van Slyke, D. D., and Cullen, G. E.: *A Permanent Preparation of Urease and Its Use in the Determination of Urea*, *Jour. Biol. Chem.*, 1914, **19**, 211.

7. Folin, O., and Denis, W.: *Nitrogen Determination by Direct Nesslerization. Nonprotein Nitrogen in the Blood*. *Jour. Biol. Chem.*, 1916, **26**, 491.

8. Goodall, H. W.: *An Accurate Rapid Method for the Determination of Chlorid in the Urine. A Critical Study of Short Methodism Vogue*. *Boston Med. and Surg. Jour.*, 1909, **160**, 304.

Dec. 2 and 23, 1916. Urine clear, amber, acid; specific gravity 1.015 and 1.022; slightest possible trace of albumin with the heat and acetic acid test; a rare hyaline or granular cast; no pus cells, no erythrocytes, no epithelium.

Oct. 31 and Nov. 2, 1916. Urine clear, amber, acid; specific gravity 1.015; no albumin, no casts, no erythrocytes, no pus cells, no epithelium.

Phthalein excretion: Dec. 1, 1916, 72 per cent. in two hours. The percentage of purin nitrogen in sweetbreads fed which was excreted as uric acid nitrogen was 13.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Nonpro- tein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
1916 Dec. 14	Purin-free diet begun
14	44.4	1.7	
15-16	7 a. m. - 7 a. m.	1,110	0.53			
16-17	760	0.48			
17-18	435	0.27			
18-19	790	0.41			
19-20	670	0.35			
20-21	595	0.33			
21-22	675	0.37			
22	7 a. m. - 1 p. m. 12 N. 1 p. m. 7 p. m.	130	0.06	40.0 45.6 1.9	150 gm. sweet- breads
22-23	950	0.63			
23	12 N.	41.3	1.4	
23-24	505	0.28			
24-25	1 p. m. - 1 p. m.	620	0.38			

Endogenous output of uric acid December 18-22 = 1.73 gm.

Endogenous output of uric acid per day = 0.35 gm.

Exogenous output of uric acid December 23 = 0.28 gm.

Percentage of purin nitrogen in 150 gm. of sweetbreads according to Burian and Schur = 0.68 gm.

Per cent. of purin nitrogen excreted as uric acid nitrogen = 13.

EFFECT OF A MEAL OF SWEETBREADS ON THE URIC ACID AND NONPROTEIN NITROGEN IN THE BLOOD

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonpro- tein N per 100 C.c. Blood	Diet of Patient	Remarks
1916 Dec. 14	1.7	44.4	Mixed	Purin-free diet begun
22	...	40.0	Purin-free	
	1.9	45.5	Purin-free	7 hours after a 150 gm. sweetbread meal
23	1.4	41.3	Purin-free	

Summary: The blood uric acid is normal. There is a moderate retention of nonprotein nitrogen with the patient on a mixed diet. No noteworthy retention of nonprotein nitrogen is present after the sweetbread meal.

Summary of Case 1.—Two of three urine specimens examined contained a scant trace of albumin and a rare cast. The significance of these findings will be discussed with those of the following cases. Phthalein excretion was normal. The amount of uric acid eliminated was small. There was a slight but definite increase of total nonprotein nitrogen in the blood when the patient was on a mixed diet. This function can be elicited other than that manifested by the diminution may explain the low output of exogenous uric acid. There was no noteworthy retention of nonprotein nitrogen in the blood after the meal of 150 gm. of sweetbreads, in spite of the fact that retention had occurred when the patient was on a mixed diet.

CASE 2.—W. H. K., Medical No. 5278. Woman, white, aged 29.

Diagnosis: Chronic arthritis.

The patient's habits were good. She had had chronic polyarthritis with occasional fairly acute exacerbations for the previous two years. The joints never had been either severely painful or tender. During the previous six months stiffness of the knees had prevented walking. Physical examination was negative except for the joints. There was limitation of motion and crepitation in all joints of the extremities. The elbows, wrists, finger joints, knees, and joints of both halluxes were enlarged, principally as the result of thickening of the periarticular tissues. Blood pressure was 110 mm. systolic and 75 mm. diastolic. Urine examinations were negative except for a scant trace of albumin and a rare cast in one of the specimens. Phthalein excretion was 65 per cent. in two hours.

TWO-HOUR RENAL TEST. NOV. 5, 1916

Time	Volume of Urine in C.c.	Specific Gravity	Nitrogen		Chlorids	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	61	1.015	0.67	0.41	0.54	0.33
9 a.m. - 11 a.m.	72	1.015	0.89	0.64	0.33	0.24
11 a.m. - 1 p.m.	75	1.015	0.77	0.58	0.33	0.25
1 p.m. - 3 p.m.	238	1.010	0.36	0.84	0.18	0.42
3 p.m. - 5 p.m.	237	1.008	0.30	0.71	0.14	0.33
5 p.m. - 7 p.m.	80	1.014	0.63	0.50	0.20	0.16
7 p.m. - 7 a.m.	605	1.012	0.50	3.03	0.28	1.69

Summary of two-hour renal test: Water: no fixation of amount. Increased amount of night urine. Slight fixation of specific gravity. Nitrogen, no fixation. Sodium chlorids, no fixation.

Clinical pathologic findings in the urine: Sept. 13 and 14, 1916. Urine straw colored, slightly turbid, acid; specific gravity 1.012; slightest possible trace of albumin with the heat and acetic acid test; a rare hyaline cast, a few pus and squamous epithelial cells, no erythrocytes. October 3, 12, 22, 25, 26, 27, November 8, 9, 20, and December 2 and 17. Urine straw colored; slightly turbid; acid; specific gravity 1.004 to 1.008. No albumin, no casts, a few pus cells, numerous squamous epithelial cells, no erythrocytes.

Phthalein excretion: Dec. 1, 1916, 65 per cent. in two hours.

McLean index of urea excretion: Nov. 28, 1916, 95.2 per cent.

Percentage excretion of intravenously injected uric acid: Nov. 9 and 12, 1916, 40 per cent.

Percentage of purin base nitrogen of sweetbreads ingested excreted as uric acid nitrogen: Nov. 22 to 24, 1916, 30 per cent.

UREA N, NONPROTEIN AND URIC ACID OF THE BLOOD

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient
1916 Oct. 31	1.8	Mixed
Nov. 8	1.6	Purin-free
8	1.5	27.9	Purin-free
22	1.5	Purin-free
27	16.3	Mixed

Summary: The uric acid, nonprotein and urea nitrogen are not increased.

CASE 3.—J. G., Medical No. 5421. White, man, aged 43.

Diagnosis: Gout; arteriosclerosis; hypertension; chronic myocarditis; very questionable chronic nephritis.

The patient had used beer freely. He had about sixteen attacks of severe polyarthrits of gouty character during the previous twenty-six years. Physical examination showed numerous tophi in the ears and on the fingers. The joints showed no changes of chronic arthritis. The radial artery walls were sclerosed. The blood pressure was 185 mm. systolic and 117 mm. diastolic. Otherwise physical examination was negative. The urine examination was negative. Phthalein excretion was 53 per cent. in two hours.

Clinical pathologic findings in the urine: Oct. 11, 12, 13, and Nov. 13, 1916. Urine clear, amber, acid; specific gravity 1.014; no albumin with the heat and acetic acid test; no pathologic formed elements.

TWO-HOUR RENAL TEST, Nov. 28, 1916

Time	Volume of Urine in C.c.	Specific Gravity	Nitrogen		Chlorids	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	183	1.020	0.39	0.51	0.78	1.04
9 a.m. -11 a.m.	140	1.015	0.37	0.50	0.66	0.92
11 a.m. - 1 p.m.	158	1.017	0.40	0.63	0.83	1.31
1 p.m. - 3 p.m.	105	1.022	0.37	0.39	0.84	0.88
3 p.m. - 5 p.m.	150	1.008	0.47	0.70	0.97	1.46
5 p.m. - 7 p.m.	260	1.014	0.41	1.07	0.98	2.55
7 p.m. - 9 p.m.	45	1.018	0.52	0.23	0.91	0.41
9 p.m. - 7 a.m.	390	1.016	0.45	1.76	0.96	3.74

Summary of the two-hour renal test: Water: no fixation of volume; slight relative increase in the night amount; no fixation of specific gravity. Nitrogen: slight tendency toward fixation toward afternoon fixation of percentage concentration; no fixation of amount.

March 23 and 28, 1917. Urine clear, amber, acid; specific gravity 1.013; slightest possible trace of albumin, a small number of leukocytes, no epithelial cells, no erythrocytes, no casts.

March 25, 1917. Urine clear, amber; specific gravity 1.009; slightest possible trace of albumin; a rare cast; no erythrocytes, no leukocytes, no epithelial cells.

Phthalein excretion: Oct. 11, 1916, 43 per cent. in two hours; Nov. 6, 1916, 52 per cent. in two hours; March 28, 1917, 42 per cent. in two hours.

McLean index of urea excretion: Nov. 6, 1916, 41 per cent.; March 31, 1917, 1.6 per cent.; April 10, 1917, 2.4 per cent.

UREA N, NONPROTEIN N, AND URIC ACID OF THE BLOOD IN THIS PATIENT
WITH GOUT

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient	Remarks
1916 Oct. 10	6.4	Mixed	Three days prior to an acute attack of gout Acute gout attack
17	5.4	Purin-free	
30	4.1	Purin-free	
Dec. 6	4.0	38.4	11.2	Mixed	
7	4.3	39.0	11.0	Mixed	
1917 March 31	13	Purin-free	
April 2	...	33.0	Purin-free	
4	Purin-free	12 noon, 150 gm. sweetbread eaten
5	...	38.7 37.3 14.4 Purin-free	7 p. m., 11 a. m., 12 noon, 150 gm. sweetbread eaten
6	...	39.8	Purin-free	11 a. m.,
7	12 noon, 150 gm. sweetbread eaten
8	10.1	12 noon, 150 gm. sweetbread eaten
9	...	37.5			

Summary: The blood uric acid is high. The urea nitrogen is not increased. The nonprotein nitrogen shows a slight increase after the feeding of sweetbreads.

Summary of Case 3.—The evidences of depressed renal function in this case are the low index of urea excretion and the increase in the amount of night urine. The other findings by the two-hour renal test, the slightly lowered phthalein excretion and the slight increase in nonprotein nitrogen are only suggestive of a disturbance in renal function. No abnormal retention of nonprotein nitrogen in the blood occurred after feeding sweetbreads for five days. It is theoretically possible that there is a type of pathologic kidney in which no disturbance in function can be elicited other than that manifested by the diminution in the excretion of uric acid. This case approaches that type more nearly than any of the others studied. The findings in this case do not show indisputable evidence of depressed renal function, but they are strongly indicative of such a condition.

CASE 4.—W. P. G., Medical No. 5471. Negro, man, aged 43.

Diagnosis: Gout; very questionable chronic nephritis.

The patient's habits were good. During the previous ten years he had had a dozen attacks of gout affecting the joints of the lower extremities and of the phalanges of the fingers. On physical examination numerous tophi were found in the ears and about the finger joints. Otherwise, physical examination was negative. The blood pressure was 135 mm. systolic and 95 diastolic. The urine contained no casts, no blood and no epithelium. A scant trace of albumin was found once in the examination of several urine specimens. Phthalein excretion was 42 per cent. in two hours.

Clinical pathologic findings in the urine: Oct. 20, 1916. Urine clear, amber, acid; specific gravity 1.010; the slightest possible trace of albumin with the heat and acetic acid test; no pathologic formed elements. Oct. 21, Nov. 1 and 12, 1916. Urine clear, amber; specific gravity 1.012; no pathologic findings.

Phthalein excretion: Nov. 10, 1916, 42 per cent. in two hours.

McLean index of urea excretion: Nov. 9, 1916, 15.5 per cent.

Percentage excretion of intravenously injected uric acid: Oct. 29, 1916, 14 per cent.

TWO-HOUR RENAL TEST, NOV. 9, 1916

Time	Volume of Urine in C.c.	Specific Gravity	Nitrogen		Chlorids	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	110	1.014	0.62	0.68	0.55	0.61
9 a.m. - 11 a.m.	74	1.016	0.77	0.57	4.28	1.21
11 a.m. - 1 p.m.	67	1.015	0.75	0.51	0.22	0.15
1 p.m. - 3 p.m.	72	1.014	0.76	0.55	0.38	0.27
3 p.m. - 5 p.m.	72	1.016	0.74	0.53	0.35	0.25
5 p.m. - 7 p.m.	47	1.015	0.74	0.35	0.22	0.10
7 p.m. - 9 p.m.	95	1.016	0.77	0.73	0.20	0.20
9 p.m. - 7 a.m.	440	1.014	0.72	3.17	0.35	1.54

Summary of two-hour renal test: Water: specific gravity fixed; amount not fixed; relative increase in the amount of night urine. Nitrogen: considerable fixation of the percentage concentration and of the amount. Sodium chlorid: some fixation of the percentage concentration and of the amount.

UREA N, NONPROTEIN N, AND URIC ACID OF THE BLOOD IN GOUT

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient
1916 Oct. 23	3.3	43.5	Purin-free
27	4.1	Purin-free
28	4.3	Purin-free
Nov. 29	4.3	49.5	30.3	Mixed

Summary: The blood uric acid is high. There is a definite retention of urea and of nonprotein nitrogen.

Summary of Case 4.—There was the slightest trace of albumin in one of four urines examined. The renal function studies showed a small diminution in the phthalein output, a very low index of urea excretion, a moderate but definite retention of both urea and non-protein nitrogen in the blood and a fixation of specific gravity, a relative increase in the amount of night urine and a fixation of the nitrogen output in the two-hour test. These findings are definite evidences of a considerable disturbance in the function of the kidneys.

CASE 5.—A. L. E., Medical No. 5297. White, man, aged 48.

Diagnosis: Gout; cirrhosis of the liver; questionable nephritis.

The patient had used large quantities of beer and whisky for many years. In the previous five years the patient had had five attacks resembling more the exacerbations of a chronic arthritis than gout. Three of these attacks occurred in the Peter Bent Brigham Hospital. Physical examination showed several tophi in the ears. Blood pressure was 156 mm. systolic and 96 mm. diastolic. The liver edge was palpable 4 cm. below the right costal margin. Otherwise the physical examination was negative. The urine showed occasionally a scant trace of albumin and a few casts. Phthalein excretion was 24 per cent. in two hours.

Clinical pathologic findings in the urine: Five urine examinations were made between Sept. 14 and Oct. 1, 1916. The specific gravity varied between 1.007 and 1.020. Three specimens contained the slightest possible trace of albumin with the heat and acetic acid test, and the other two, none. An occasional hyaline or granular cast, but no other pathologic elements as found in the specimens of urine. Six subsequent urine examinations were made between Oct. 1 and Nov. 24, 1916. No albumin, no casts, no erythrocytes, no pus, and no epithelium were found.

Phthalein excretion: Sept. 18, 1916, 24 per cent. in two hours.

McLean index of urea excretion: Sept. 18, 1916, 25 per cent.; Nov. 14, 1916, 15 per cent.

Percentage of purin nitrogen administered which was excreted as uric acid nitrogen: Nov. 26 and 27, 1916, 5.1 per cent.

TWO-HOUR RENAL TEST, Nov. 14, 1916

Time	Volume of Urine in C.c.	Specific Gravity	Nitrogen		Ohlorids	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	19	1.030	0.98	0.19	0.40	0.08
9 a.m. - 11 a.m.	70	1.014	0.71	0.50	0.32	0.22
11 a.m. - 1 p.m.	33	1.024	1.19	0.39	0.44	0.15
1 p.m. - 3 p.m.	38	1.022	1.17	0.45	0.36	0.15
3 p.m. - 5 p.m.	16	1.024	1.32	0.21	0.44	0.07
5 p.m. - 7 p.m.	40	1.022	1.02	0.41	0.26	0.10
7 p.m. - 9 p.m.	40	1.018	0.92	0.37	0.24	0.10
8 p.m. - 7 a.m.	235	1.018	1.01	2.37	0.43	1.11

Summary of the two-hour renal test: Water: no fixation of amount but the output was small. No fixation of specific gravity. Output of night urine relatively increased. Nitrogen: no fixation. Sodium chlorid: no fixation.

UREA N, NONPROTEIN N, AND URIC ACID OF BLOOD IN GOUT

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient	Remarks
1916 Oct. 15	4.6	Purin-free	Acute attack of gout Seven hours after a meal of 150 gm. sweetbreads
Nov. 3	3.5	52.6	Purin-free	
14	27.5	Purin-free	
25	4.5	54.3	Purin-free	
	5.3	74.3	Purin-free	
26	4.8	73.0	Purin-free	
Dec. 4	5.3	66.6	Mixed	

Summary: The blood uric acid and urea nitrogen are high. There is a retention of nonprotein nitrogen especially marked after the sweetbread meal.

Summary of Case 5.—The occasionally slight trace of albumin and rare casts found in the urine in this case were present during or near the time the patient was suffering with a gouty attack. Definite evidences of depression of renal function are the low phthalein excretion, the decrease in the index of urea excretion, a relative increase in the amount of night urine in the two-hour test, the increase in urea and nonprotein nitrogen in the blood, and the retention of nonprotein nitrogen after feeding 150 mg. of sweetbreads. These findings show very conclusively that there was a marked disturbance in the functional capacity of the kidney. But whether or not these findings justify the diagnosis of chronic nephritis is at present not known.

CASE 6.—J. F. S., white, man, aged 42.

Diagnosis: Gout.

The patient was a heavy beer drinker. He had had numerous attacks of monoarticular and of polyarticular arthritis of typical gouty character in the previous ten years. Physical examination was negative except for tophi in the ears, about the knuckle joints of the left hand and just above the olecranon processes of both ulnae. There were no evidences of cardiovascular disease. Blood pressure was 144 mm. systolic and 90 mm. diastolic.

Clinical-pathologic findings in the urine: Feb. 4, 1917. Urine: amount, 2,200 c.c.; clear, amber, acid; specific gravity 1.020; no albumin with the heat and acetic acid test; an occasional hyaline cast; a few pus cells; no epithelium, no erythrocytes. Feb. 17, 1917. Urine clear, yellow, acid; specific gravity 1.017; slightest possible trace of albumin with the heat and acetic acid test; no casts, no epithelium, no erythrocytes; a moderate number of pus cells. Feb. 18, 1917. Urine clear, yellow, acid; specific gravity 1.018; slightest possible trace of albumin with the heat and acetic acid test; no erythrocytes; a moderate number of pus cells; no epithelium.

Phthalein excretion: Jan. 30, 1917, 15 per cent. in two hours; Feb. 9, 1917, 38 per cent. in two hours.

McLean index of urea excretion: Feb. 5, 1917, 29.5 per cent.; Feb. 18, 1917, 22.5 per cent.

TWO-HOUR RENAL TEST, FEB. 11, 1917

Time	Water, C.c.	Specific Gravity	Nitrogen		Salt	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	174	1.017	0.31	0.54	0.87	1.69
9 a.m. - 11 a.m.	87	1.017	0.36	0.31	0.68	0.59
11 a.m. - 1 p.m.	90	1.019	0.42	0.41	0.69	0.69
1 p.m. - 3 p.m.	231	1.018	0.28	0.64	0.83	1.91
3 p.m. - 5 p.m.	232	1.017	0.34	0.67	0.81	1.88
5 p.m. - 7 p.m.	241	1.019	0.40	0.97	0.90	2.17
7 p.m. - 9 p.m.	233	1.019	0.55	1.31	0.74	1.72
9 p.m. - 7 a.m.	423	1.017	0.53	0.22	0.78	3.30

Summary of two-hour renal test: Water: fixation of specific gravity at a high level; afternoon fixation of amount; night amount relatively increased. Nitrogen: no fixation. Sodium chlorid: slight fixation of percentage concentration; no fixation of amount.

URIC ACID, UREA AND NONPROTEIN NITROGEN OF THE BLOOD IN GOUT

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonpro- tein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient	Remarks
1917 Jan. 30	5.8	47.6	Mixed	
Feb. 5	...	44.6	25.3	Purin-free	
22	27.4	Purin-free	11 a.m. and 11:15 a.m., patient given 150 gm. sweetbreads
		43.5	28.9	Purin-free	6 p. m., same
23	...	48.8	36.6	Purin-free	11 a. m., same

Summary: The uric acid and nonprotein nitrogen are increased with the patient on a mixed diet. A retention of nonprotein nitrogen follows the sweetbread meal.

Summary of Case 6.—A few casts were found in the urine on two of four examinations. The scant trace of albumin occasionally present may be accounted for by the pus cells which were found. The diagnosis of nephritis was not made in this patient. The evidences of depression in renal function are the low phthalein output, the low index of urea excretion, the retention of nonprotein nitrogen in the blood on a mixed diet and the retention of both nonprotein and urea nitrogen after the sweetbread meal.

CASE 7.—F. J. S., Medical No. 6151. White, man, aged 43.

Diagnosis: Gout; obesity.

The patient's habits were good. During the past ten years he had had numerous attacks of arthritis either in one or both of the lower extremities. Physical examination was essentially negative. There were no signs of cardiovascular

disease. Blood pressure was 130 mm. systolic and 90 mm. diastolic. A tophus was present in the right ear and from it sodium urate crystals were obtained.

Clinical pathologic examination of the urine: Feb. 19, 1917. Urine clear, amber, acid; specific gravity 1.022, slightest possible trace of albumin with the heat and acetic acid test; no pathologic formed elements. Feb. 25, 1917. Urine examination negative. March 3, 1917. Urine clear, amber, acid; specific gravity 1.011; no albumin, no sugar; one hyaline cast found; no other formed elements present.

Phthalein excretion: Feb. 17, 1917, 50 per cent. in two hours; March 1, 1917, 21 per cent. in two hours.

McLean index of urea excretion: Feb. 17, 1917, 44.2 per cent.; Feb. 27, 1917, 16.2 per cent.; March 1, 1917, 35.7 per cent.

TWO-HOUR RENAL TEST, FEB. 22, 1917

Time	Water, C.c.	Specific Gravity	Nitrogen		Salt	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	88	1.027	1.26	1.11	0.50	0.44
9 a.m. - 11 a.m.	96	1.025	1.02	1.56	0.40	0.42
11 a.m. - 1 p.m.	107	1.025	1.21	1.30	0.57	0.61
1 p.m. - 3 p.m.	99	1.024	1.22	1.21	0.33	0.33
3 p.m. - 5 p.m.	109	1.023	1.32	1.44	0.41	0.45
5 p.m. - 7 p.m.	155	1.019	0.79	1.26	0.46	0.73
7 p.m. - 9 p.m.	142	1.020	0.87	1.28	0.52	0.74
9 p.m. - 7 a.m.	511	1.020	1.03	5.26	0.46	0.24

Summary of two-hour renal test: Water: no fixation of amount; tendency toward fixation of specific gravity but ability to concentrate retained; night amount increased. Nitrogen: no fixation. Sodium chlorid: no fixation.

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonpro- tein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient	Remarks
1917 Feb. 17	24.7	Mixed	Very little meat in diet
23	4.9	43.6	25.8	Purin-free	10 a. m.; 11 a. m., pa- tient received 150 gm. sweetbreads
		57.9	32.4	Purin-free	6 p. m.
24	...	50.0	28.8	Purin-free	11 a. m.
27	...	55.5	28.3	Purin-free	

Summary: The blood uric acid is increased. There is a retention of non-protein nitrogen and to a less extent of urea nitrogen, both being considerably increased for several days after the sweetbread meal.

Summary of Case 7.—The scant trace of albumin and the one cast found in the urine were present at a time when the patient was febrile during an attack of gout. There were no signs of chronic nephritis in this patient. The evidences of depressed renal function are the low

phthalein output and the low index of urea excretion, the increased amount of night urine in the two-hour test, and the retention of urea and nonprotein nitrogen in the blood after the sweetbread meal. These findings show a definite derangement in the function of the kidneys.

SUMMARY OF THE RENAL FUNCTION IN GOUT

We have studied the renal function in two nongouty and in five gouty patients with tophi. The more important findings obtained in the gouty persons are given in the accompanying table.

TABLE GIVING SYNOPSIS OF THE FINDINGS BY THE RENAL FUNCTION TEST IN GOUT

Case	Phthal- ein Excre- tion, per Cent.	McLean Index, per Cent.	Mg. Non- protein N per 100 C.e. of Blood	Mg. Urea N per 100 C.e. of Blood	Mg. Non- protein N per 100 C.e. Blood after Sweet- breads	Excre- tion of Exoge- nous Urie Acid in per Cent.	Positive Findings in Two-hour Renal Test
3	43 52 42	41.0 1.6 2.4	39.0	11.9	37.3	0	Increased amount of night urine
4	42	15.5	49.5	30.3	14	Fixation of specific gravity, of amount and percentage con- centration of N
5	24	25	54.3	27.5	74.3	0	Relative increase of night urine
6	15 38	29.5 22.5	47.6 44.6 25.3	.. 48.8	Fixation of specific gravity Night amount rela- tively increased
7	50 21	44.2 16.2 35.7	28.8	50.0	..	Increased amount of night urine

The table shows that a considerable variation existed in the findings obtained by the tests for renal function both among the different cases and in the same case. Nevertheless, the results obtained by a series of any one test were consistent in the same case. There was considerable increase in both the nonprotein and urea nitrogens in the blood in all but one case. The McLean index of urea excretion was much below the normal in all cases. The two-hour renal test gave definite evidences of disturbed renal function in four cases and suggestive evidence in one.

A scant trace of albumin was present in one urine of Case 4. In the remaining five cases of gout scant traces of albumin and a few casts were present in certain of the urine specimens. It will be noted that similar findings were obtained in two nongouty, nonnephritic cases (1 and 2). The occasional finding of scant traces of albumin and a

small number of casts in the urine is not considered as indicative of chronic nephritis. Such urinary findings, although evidence of temporary renal damage, are too commonly present in pathologic conditions not connected with kidney lesions to be interpreted as the result of a chronic nephritis. The question of the existence of that disease in our cases of gout was raised by the abnormal findings in the studies of renal function.

To the list of renal function tests has been added the study of the total nonprotein nitrogen in the blood after a meal of 150 gm. of sweetbreads. The amounts fed were not unduly large and should cause no rise in the nonprotein nitrogen in the blood in a person with normal kidneys. No retention of this nitrogen occurred in the patient with alcoholic cirrhosis (Case 4) in spite of the fact that a slight increase was present on a mixed diet. Likewise no retention of nonprotein nitrogen in the blood was found after a meal of 150 gm. of sweetbreads in a case of acute infectious arthritis and congenital heart disease, and also in gout (Case 3). The patient with arthritis was chosen because of the constant presence of a scant trace of albumin and casts in the urine. The amounts of nonprotein nitrogen in the blood in this case were 37.5 mg. before the sweetbread meal and 40 mg. twenty-four hours afterward.

In all the cases of gout there was definite depression of renal function as measured by some of the tests. It is, therefore, fair to assume that the diminution in or the absence of excretion of exogenous uric acid and of other nitrogenous substances in these cases of gout may be due to renal retention and not to the result of derangements in the intermediary metabolism of the nucleins. These cases, however, do not exclude the possibility that the decreased renal function is secondary to the gout and that the uric acid retention was present before there were signs of retention of other nitrogenous substances. It is important to know whether disturbances in renal function occur in the first stages of gout. We have not had early cases for study. In such cases there would be the uncertainty of knowing whether they were really gout or not, since the only pathognomonic sign is the deposition of sodium urate crystals, and this is a late manifestation.

SUMMARY AND DISCUSSION

The apparently frequent occurrence of decreased renal function in cases of typical gout justifies a word of caution against assuming that the faulty excretion of uric acid and of other nitrogenous substances when found is due to derangements in metabolism. It may be due to renal retention as was suggested by Garrod⁹ in 1848. Whichever

9. Garrod, A. B.: Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease, *Med.-Chirurg. Trans.*, 1848, **31**, 83.

happens, uric acid may still be the cause of the symptoms or at least closely related to them. The theories of Umber,¹⁰ Brugsch and Schittenhelm,¹¹ Minkowski¹² and others regarding the rôle of the nuclein metabolism and of uric acid in the etiology of gout grow untenable in proportion to the evidence of a deranged renal excretion in gouty persons. Umber advanced the hypothesis that the failure of gouty persons to excrete exogenous uric acid was due to a special affinity of the tissues for uric acid. On the other hand, Minkowski offered the explanation that the uric acid entered into chemical combinations in the blood which prevented its excretion by the kidneys. Chemical methods are not available for the proof or disproof of the theories of either of these two authors. But the finding of deficiency in the renal function of gout offers a simpler explanation for the phenomenon. A. E. Garrod¹ says: "If the fault is in the kidneys alone, gout must be removed once and for all from the category of metabolic disorders and placed among the sequelae of renal inadequacy, at least in so far as the uric acid phenomena of the disease are concerned."

Kionka¹³ revived the theory that gout was the result of functional disturbances of the liver. This was based on the finding that glycocoll accelerated the precipitation of a monourate from a solution of biurate, and on the observation that glycocoll had been found in the urine of gouty persons. Frey¹⁴ attempted to prove Kionka's theory by certain experimental work, but Abderhalden and Schittenhelm¹⁵ have shown that his results were erroneous. Hirschstein¹⁶ reported that glycocoll was present in the urine of gouty patients in much greater quantities than in health. On the basis of Hirschstein's work, Umber has concluded that there is a disturbance in the intermediary metabolism in gout. Samuely¹⁷ was unable to confirm Hirschstein's findings regarding the derivation of glycocoll from uric acid. The method used by Hirschstein to determine the amount of glycocoll in the urine is not

10. Umber, F.: Ernährung und Stoffwechselkrankheiten. Berlin, 1914.

11. Brugsch, T., and Schittenhelm, A.: Die Nukleinstoffwechsel und seine Störungen.

12. Minkowski, O.: H. Nothnagel's spezielle Path. u. Therap., 1903, 7, 202.

13. Kionka, H.: Glykokoll und Harnstoff in ihren Beziehungen zur Harnsäure. Eine theorie der Gicht. Ztschr. f. exper. Path. u. Therap., 1905-1906, 2, 17.

14. Frey, E.: Physikalisch-chemisches Verhalten des Glykokolls und Harnstoff bei der Gicht. Ztschr. f. exper. Path. u. Therap., 1905-1906, 2, 26.

15. Abderhalden, E., and Schittenhelm, A.: Bemerkungen zu den Arbeiten von Frey über die Rolle des Glykokolls bei der Entstehung der Gicht. Ztschr. f. exper. Path. u. Therap., 1905-1906, 2, 431.

16. Hirschstein, L.: Die Beziehungen des Glykokolls zur Harnsäure. Ztschr. f. exper. Path. u. Therap., 1907, 4, 118.

17. Samuely, F.: Bemerkung zu der Arbeit von L. Hirschstein: die Beziehungen des Glykokolls zur Harnsäure. Ztschr. f. exper. Path. u. Therap., 1907, 4, 558.

quantitative,¹⁸ and this renders his findings questionable. Furthermore, the connection between uric acid and glycocoll as advanced in the theory proposed by Umber is questionable, since the human organism does not decompose uric acid. To accept Umber's theory requires the assumption of the development of new and complex factors in intermediary metabolism, for which there is no satisfactory evidence.

Brugsch and Schittenhelm have upheld the view that in gout there is a disturbance in the intermediary metabolism of the nucleins. Their most important experimental findings have been verified by Levene and Kristeller¹⁹ in this country. The considerations which led Brugsch and Schittenhelm to formulate their theory of the etiology of gout are as follows:

1. The endogenous output of uric acid in gout is less than in normal man, but the amount in the blood is greater. They concluded from these findings that there was a retarded uric acid destruction in the gouty person.

2. If purin or nuclein containing materials were added to the purin-free diet of a gouty patient the elimination of exogenous uric acid was lower in quantity and more protracted in time than in health. From these findings they formed the hypothesis that there was a retarded formation and a retarded elimination of uric acid in gout.

The above conclusions drawn by these two investigators concerning the rôle of nucleins in the production of gout become doubtful for the following reasons:

1. It is generally agreed that uric acid cannot be destroyed by the human organism.²⁰

2. Pratt and I²¹ have shown that a protracted elimination of exogenous uric acid is not peculiar to gout.

18. Samuely, F.: See Footnote 17. Fischer, E., and Bergell, P.: Ueber die Derivate einiger Dipeptide und ihr Verhalten gegen Pankreas-fermente. *Berichte d. deutsch. chem. Gesellsch.*, 1903, **36**, 2593. Abderhalden, E., and Bergell, P.: Ueber das Auftreten von Monoaminosäuren im Harn von Kaninchen nach Phosphorvergiftung. *Ztschr. f. physiol. Chem.*, 1903, **39**, 464. Brugsch, T., and Schittenhelm, A.: Ueber den Abbau von Glykokoll und Alanin beim gesunden und gichtkranken Menschen. *Ztschr. f. exper. Path. u. Therap.*, 1907, **4**, 538.

19. Levene, P. A., and Kristeller, L.: Nitrogen and Nuclein Metabolism in Gout. *Jour. Exper. Med.*, 1912, **16**, 303.

20. Soetbeer, F., and Ibrahim, J.: Ueber das Schicksal eingeführter Harnsäure im menschlichen Organismus. *Ztschr. f. physiol. Chem.*, 1902, **35**, 1. Wiechowski, W.: Ueber die Zersetzlichkeit der Harnsäure im menschlichen Organismus. *Arch. f. exper. Path. u. Pharmakol.*, 1908-1909, **60**, 185. Wells, H. G.: Some Additions to Our Knowledge of Purin Metabolism and Their Bearing on the Problem of Gout. *Internat. Clin.*, 1916, **26**, 319. Jones, W.: *Nuclein Acids, Their Chemical Properties and Physiological Conduct. Monographs on Biochemistry*, New York, 1914.

21. To be published.

3. In the investigation here presented it has been shown that the kidney in gouty patients usually is functionally deficient, and this can explain the low output of exogenous uric acid in gout.

Although the considerations advanced in support of the theory of Brugsch and Schittenhelm may have other explanations as noted above, nevertheless their contention with regard to a relation between nuclein metabolism and gout is not disproved.

The purpose of this discussion has been to emphasize the facts that (1) many of the findings which have heretofore been considered due to disturbances of nuclein metabolism in gout may be explained as the result of renal inadequacy, and (2) that the theories concerning the etiology of gout remain hypotheses without satisfactory experimental bases.

The finding of renal deficiency in gouty persons renders the value of the study of exogenous uric acid elimination as an aid in the diagnosis of gout questionable. Before the status of exogenous uric acid excretion as a symptom of gout can be established a study of the output of uric acid in the different types of nephritis must be made.

CONCLUSIONS

1. The gouty kidney is often functionally deficient.
2. The faulty elimination of exogenous uric acid and of other nitrogenous substances by gouty persons may be the result of depression of the functional power of the kidneys.
3. While renal retention explains many of the anomalies occurring in the excretion of uric acid and of other nitrogenous substances in gout, nevertheless this does not explain the nature of gout, nor does it preclude the possibility of there being an underlying perversion of metabolism.

I am indebted to Dr. B. Smith of Los Angeles, and to Drs. J. P. O'Hare and E. Smith for assistance in certain of the renal function tests. I wish to express my thanks to Dr. H. A. Christian for many helpful suggestions. I am indebted to Dr. Otto Folin for advice as to chemical methods. Dr. A. A. Hornor was kind enough to send me one of the cases from the Boston City Hospital.

AMYOTONIA CONGENITA OF OPPENHEIM

A REPORT OF SIX CASES, WITH A FULL REVIEW OF THE LITERATURE *

MARK S. REUBEN, M.D.
NEW YORK

INTRODUCTION

In 1900, Oppenheim¹ called attention to a syndrome which has since been designated as "Oppenheim's Disease."

He had repeatedly observed, in the first months of infancy, and during the first and second years of life, a disease with which he was not acquainted and one of which he could find no mention in the literature.

In this disease he observed immobility of the whole body, or of certain parts of the body, especially of the lower extremities; the parts affected were flaccid; the main symptom was the striking flaccidity, hypotonia or atony of the muscles, which was associated with complete loss or with very much diminished tendon reflexes. In most cases only the legs were affected; in one 8-month-old infant the muscles of the back and the neck were also affected; the child could not sit up nor support its head upright. The muscles of the eyes, tongue and deglutition did not become involved; the diaphragm functionated properly; the intercostal muscles on the contrary seemed to be affected.

The muscles felt flaccid and soft; they appeared thin and devoid of fat, but they did not give the impression of the presence of atrophy.

The electrical reactions showed a quantitative diminution up to complete loss of electrical irritability.

The intelligence, the sensations and the cerebral functions were not disturbed; from the symptoms it appeared to him that he was dealing with a congenital syndrome, even though the symptoms did not always manifest themselves at birth.

He believes that in this disease he was not dealing with an affection of the central nervous system, but with a primary muscle disease, which is due to a delayed and arrested development of the musculature; he does not, however, exclude the possibility that the primary seat of the delayed development may be in the anterior horn cells and not in the muscles; this condition is subject to more or less complete

* Submitted for publication April 30, 1917.

1. Oppenheim: On General and Localized Atony of the Muscles (Myotonie) in Young Children. *Monatschr. f. Psychiat. u. Neurol.*, 1900, 8, 232.

The number of the pregnancy of which the patient was born was given in forty-three instances; the patient was:

The first born in nine cases
The second born in thirteen cases
The third born in eight cases
The fourth born in four cases
The fifth born in three cases
The sixth born in no case
The seventh born in three cases
The eighth born in one case
The ninth born in one case
The tenth born in one case

Thus, of forty-three cases, the patients were the offspring of early pregnancies (first three) in thirty cases (70 per cent.); it is evident that these figures contravert the accepted idea that this disease is due to reproductive exhaustion.

The family history was usually negative; the Wassermann reaction was positive in only two cases (Brunard and Gordon, both doubtful cases); it was negative in twelve cases (Cases, 131, 127, 116, 115, 110, 107, 106, 69, 57, 53, 50, 47); the Pirquet reaction was negative in nine cases. There was a history of alcoholism in the parents in two cases (Griffith and Concetti); in a few cases, relatives of parents were afflicted with neuromuscular diseases; in one of Collier's cases, the mother was always "weak in her legs"; in Silvestri's case, the aunt of the mother died of progressive muscular dystrophia; another infant had myxedoma, and another had osteomalacia. In a small percentage of cases the disease has been familial in character; Sorgente has reported two brothers suffering from the same disease; Concetti, a brother and a sister; Skoog, two in the same family; Foot, three in the same family; Beavor, four in the same family; Collier, two in the same family, and Reuben, three sisters, all of whom died.

There was a history of convulsions in five cases: Orbison's patient began to have convulsions at 1 year; Faber's patient, during first week of life; convulsions preceded death in both of Sorgente's patients; Brunard's patient had convulsions at 2 months, and in the case of Lereboullet, the flaccidity gave rise to rigidity during convulsions.

SYMPTOMS

Inspection.—Head: In two cases the head was asymmetrical.

Face: Many have noted that face was small in proportion to head; in a number of cases it was triangular in shape; in a small percentage of the cases there was a lack of mobility of facial expression; the face lacked individuality; it was doll-like and the lines which gave expression to the face were lacking; in a few cases the mouth was held open, and chin was constantly held on the sternum.

Neck: In two cases there were contractures of the sternocleidomastoid muscles present, so that the head was turned to one side.

Arms and Hands: In the typical cases the arms were held in a peculiar position; the arms were abducted; the forearms were flexed at elbow, and the hands were pronated so that the dorsum of the hands was in contact with the pelvic bones; in a few cases, the arms were abducted and the forearms were held in exaggerated supination (Zappert, Concetti, [two cases]); in several cases the arms were held in position of Erb's palsy; when contractures took place in the arms, the arms were abducted and elevated, the forearms were sharply flexed and the hands were pronated so that they came in contact with the chin (Kaumheimer).

Trunk: In prone position nothing abnormal was noted; in the sitting posture, almost all cases showed postural deformities of the spine (lordosis, scoliosis, kyphosis).

Chest: In fifteen cases, deformity of chest was noted; the most common deformity was lateral depression with elevation of the sternum; in a smaller number, there was anteroposterior flattening with excavation of the sternum (funnel shaped).

Abdomen: The abdomen was usually distended and appeared large in proportion to the chest; in twenty-eight cases the breathing was entirely abdominal and rapid (60 to 80 per minute).

Legs and Feet: In infants the thighs were partly adducted, the knees slightly flexed and the feet rotated outward; the feet were flat, long and pad-like in five cases (Charles, Gotti, Faber, Batten, Collier).

Abnormal Involuntary Movements.—Athetoid movements of the hands were noted in cases of Schippers, Cotteril, Haberman, Keersmaker, Brunard, Duthoit; tremor of the hands was noted in the cases of Purser and Snow; fibrillar twitchings, in the case of Gött; rotary movements of the head, in Feer's case, and of the hand, in Reuben's case; spasms were noted in the case of Guinon and Gauducheau (opisthotonus, a very doubtful case).

Tegumentary Status.—Vasomotor Status: Coldness and cyanosis of legs and feet were noted in three cases (136, 127, 22); marked vasomotor reactions in one case (70) and marked dermatographia in one case (112); several writers have reported a marble-like mottling of the skin of the lower extremities.

Edema: Hard or soft edema was noted in thirteen cases; in the majority of cases it was confined to the feet and legs; in one case the edema extended to the forearms and face; in the majority of the cases it is a pseudoedema, due to adiposity and difficulty of differentiation of different tissues under the skin.

General Appearance: In the great majority of cases, the patients appeared well nourished, but on weighing them it was found that in nearly all cases they were underweight and undersized; all the infants weighed less than they appeared to weigh; there was excessive adiposity in ten cases, especially three cases of Concetti, Kundt and Rothmann (legs).

Palpation.—On palpation one found that one could not differentiate between panniculus adiposis, muscles and bones; one obtained the impression that all the tissues under the skin constituted one soft flabby mass; there was no infiltration of the muscles felt anywhere; the flabbiness of the muscles varied in degrees in different muscle groups; no atrophic muscles could be felt; the deposition of fat in subcutaneous tissues was normal and masked the muscles, which were diminished in size from disuse; in a small percentage of cases adiposity was marked, especially in the gluteal regions. In a small number of cases muscle thinness amounting to atrophy was present (two cases of Batten, Collier, Marburg, Archangelsky, Councilman, Thorspecken, Coombs, Schlivelk, Gordon, Wimmer, Thompson).

Gastro-Intestinal Status.—Constipation was present in many cases, probably due to the involvement of the abdominal muscles; in a number of cases it was very obstinate and hard to relieve.

Respiratory Status.—The infants were very sensitive to affections of the lungs; in twenty-eight cases the intercostal muscles were entirely immobile, and the breathing was entirely abdominal; in these cases the breathing was very much accelerated, and in one case it was 90 respirations to the minute; in many more cases the intercostal muscles were only slightly affected.

The cardiovascular status was normal in every respect.

Rectal and vesical control was normal in all cases; in two cases there was involuntary passage of urine and feces, but there was no dribbling in either, probably due to lack of education; both of these patients were mentally backward.

Myatonic Status.—The chief symptom of this disease is hypotonia; the hypotonia varies in degree in different muscle groups; it may be so marked as to produce absolute immobility of limbs, trunk or head; it is usually most marked in the legs and least marked in the muscles innervated by the cranial nerves; it is usually widespread and affects all the skeletal muscles; all the muscle groups, however, are seldom affected to the same degree; no individual muscles in a muscle group are spared.

In not a single case was the muscular weakness absent in the lower extremities; in twelve cases the weakness was more marked in the arms; in patients under 1 year the muscles of the trunk and neck were

invariably affected. The involvement of the intercostal muscles has been mentioned. There was complete immobility of the chest noted in twenty-eight cases, and partial weakness in many more; there was weakness of the abdominal muscles in thirty-two cases; in older children there was marked improvement noted in the muscles of the arms, trunk, chest and neck; the muscles of the lower extremities showed the least tendency, and were the last to show marked improvement.

In the 128 cases in which the muscles affected were stated, the lower extremities were involved in every case; in only nine cases in which the lower extremities were affected, the upper extremities were not involved; in twelve cases the upper extremities were more affected than the lower; in thirty-one of the 128 cases, the trunk muscles were not affected; in thirty-seven of the 128 cases, the muscles of the neck were not affected or had recovered considerable power. The proximal muscles of the various muscle groups were usually more affected than the distal; in a small number the reverse was true; thus in the majority of cases there was more motor power in the toes and fingers than in the thighs and arms. The loss of power was never complete; thus in every case there was some power to move the toes and fingers, even when there was no power to move the arms, legs, trunk or head. The weakness was usually symmetrical; in cases of Zappert, Schippers, Faber and Bernhardt it was not.

In consequence of the muscular weakness, these children present a group of secondary symptoms. Weakness of the muscles of the head and neck leads to inability of holding the head upright without support and to inability to move the head in any direction; this depends on the degree of weakness of the muscles. Involvement of the muscles of the chest leads to diaphragmatic breathing and to the various deformities of the chest; when the abdominal muscles are involved, the abdomen is distended and constipation is very marked. When the arm muscles are affected, the children, when the weakness is very marked, cannot bring their hands to the mouth, only slight movements of the fingers being possible; in less severe cases, the arms can be elevated to the horizontal, but drop as if dead when the arms are elevated above the head. The legs usually show the greatest weakness; in the majority of infants only fine movements of the toes can be observed; the legs and thighs can be put in most grotesque and most uncomfortable positions, and these children are unable to correct these positions; as a result of the muscular weakness of the muscles of the feet, the feet are often long, narrow and flat, as are also the hands.

Involvement of the muscles of the spine makes it impossible for these patients to rise from the recumbent position; in older children, who have partly recovered, rising occurs in the step-ladder fashion of muscular dystrophia; when these children sit up, a number of postural

deformities become apparent, as lordosis, kyphosis and scoliosis; all these deformities usually disappear in the recumbent position.

Myasthenic Status.—The majority of these patients cannot sit up without support, or hold the head upright before the age of 2 to 4 years; the great majority do not learn to walk until they are 4 to 5 years old; in not a single case was normal walking possible; when walking is possible it is usually waddling in character, and steppage gait with ataxia is present. In cases where walking was not possible, progress was made by rolling over and over on the long axis of the body.

Of the cases reported in the literature, seventy-seven were over the age of 16 months; in these seventy-seven cases walking was possible in only thirteen cases. Walking was possible between:

- 14 months and 2 years in two cases (133, 73—doubtful cases)
- 2 years and 3 years in four cases (20, 39, 90, 118)
- 3 years and 4 years in two cases (37, 62)
- 4 years and 5 years in four cases (3, 42, 78, 88)
- 7 years and 8 years in one case (23)
- 12 years and 13 years in one case (94)
- 50 years and 51 years in one case (67)

As limited as are the movements at all the joints on active motion, as exaggerated are all the movements on passive; arms, legs and fingers can be placed in the most fantastic positions; in nearly all cases the legs can be crossed behind the back; flexion, extension, abduction, adduction and rotation are exaggerated at all the joints; they are only limited by the presence of muscular contractures; the contractures in this disease are due to unequal shortening of the various muscles.

Contractures.—These were present in thirty-seven cases, of which twenty-nine were in the lower extremities, six in the upper extremities and two in the sternocleidomastoid muscle; of the contractures in the lower extremities, sixteen were of the hamstring muscles and the knees, eight had talipes equinovarus, four of the hip and one of the back; of the six cases in which there were contractures in the upper extremities (Cases 1, 69, 77, 78, 79, 94), the contractures were usually most marked in the muscles which control the elbow; in most of these cases the arms were abducted, the elbows flexed and the hands were pronated.

In a few cases there were contractures present which could not be explained by any nerve distribution; as hyperextension of index fingers (51, 61), flexion of index finger (79) or flexion of middle fingers (108). In four cases, there were drop wrists, single or bilateral (1, 41, 51, 108).

Congenital Defects.—In addition to the six cases of congenital club-foot which were present, there were two cases of umbilical hernia (Concetti, Cotteril); one case with double inguinal hernia (Charles); dislocation of right hip, malformation of right knee and partial luxa-

tion of left thumb (Cotteril); malposition of feet (Fletcher); genu recurvatum (Gastonguay); skull deformed in two cases (156, 51); thumbs dislocated (48); winged scapular in three cases; spina bifida (19); undescended testes and rudimentary penis (Concetti); mongolian idiocy (Concetti); dislocation of shoulder (Marburg); malocclusion of the jaws was present in two cases.

Bone Changes.—In nine cases Roentgen-ray examination of the bones was made; in only one case was there marked thinning of the long bones noted (Thorspecken); in one there was delayed ossification of the wrist centers; in seven, the bone findings were normal; in three cases, the Roentgen-ray pictures of the pituitary body were normal.

Evidence of slight rickets was found in six cases (Concetti, Beling, Feer, Marburg, Schüller, Purser).

Speech.—This was not affected; the children usually began to speak at the proper time; the teething was in no way affected; in fact, in a number of cases teething was early (speech defective only in Case 42).

Cranial Nerves.—The muscles innervated by the cranial nerves were affected in many more cases than was usually supposed. The optic nerves were atrophic in Case 56 (doubtful case); cortical amaurosis was present in Cases 91, 110, 123 (no changes in the optic nerves); ptosis was present in two cases (23, 73); the orbicularis palpebrarum was toneless in Case 39; ptosis, nystagmus and strabismus was present in Case 59 (very doubtful case); convergent strabismus was noted in Cases 59, 64, 91, 110, and nystagmus in three cases (72, 98, 124).

The face was involved in twenty cases (7, 22, 23, 30, 34, 45, 47, 51, 53, 73, 84, 95, 98, 106, 108, 109, 115, 117, 124, 128); the affection of the face showed itself in the complete absence of facial expression, and immobility of the muscles; there was a statuesque or doll-like appearance of the face, and lack of corresponding expression during crying or laughing; the mouth was open, and lower jaw drooped in four cases; drooling was present in two cases (42, 53).

Deafness was noted in two cases (59, 91); swallowing was difficult and nursing was impossible in sixteen cases (1, 2, 29, 40, 41, 43, 44, 53, 95, 106, 107, 108, 109, 122, 123, 136); in four cases the infants had to be forcibly fed; the voice and crying were feeble in seven cases (32, 48, 95, 106, 108, 109, 124); automatic movements of the muscles of mastication were present in one case (32).

The eyes were rather prominent in two cases (Collier and Wilson, Laffer).

Reflexes.—No definite statement can be made as to the presence or absence of the superficial or cutaneous reflexes; in the majority of

cases they were not tested; in about 60 per cent., in which they were examined, they were normal, and in 40 per cent. they were absent.

The deep or tendon reflexes were entirely abolished in eighty-four cases; they were present but feeble in twenty-one cases, and were normal or nearly so in thirteen cases (127, 126, 114, 91, 85, 83, 73, 55, 49, 39, 20, 17, 8). The Babinski sign was positive five times (118, 112, 99, 70, 51).

In few cases were the conjunctival and the pharyngeal reflexes absent; there is no uniformity of presence or absence of the superficial or deep reflexes; they may be present in the upper extremities and absent in the lower and vice versa; they may be diminished in one part of the body and normal in another; as a rule, the knee jerks are the most uniformly absent, and the conjunctival and the pharyngeal the most uniformly present.

In six cases (as the condition improved) there was a return of knee jerks, after complete absence from birth; in not a single case was there a disappearance of deep reflexes after they once returned.

Electrical Reactions.—The electrical reactions were normal in fourteen cases (2, 3, 17, 22, 42, 45, 53, 55, 59, 67, 71, 85, 118, 123); there was diminished reaction to both galvanic and faradic currents in both nerve and muscle in fifty-two cases; there was diminished reaction to faradic current only in seventeen cases; to galvanic only, in six cases; there was no response to faradism in ten cases; no response to the galvanic current in three cases; there was no reaction to both currents in fourteen cases; in one case, there was normal reaction to faradism and diminished to galvanism, and in three cases there was normal reaction to galvanism and diminished to faradism.

In seven cases (four of which are doubtful) reaction of degeneration was found in some muscles; Rothman and Mittenheimer found partial reaction of degeneration in the lower extremities; Gött, Thorspecken, De Villa, Wimmer and Carcupino found reaction of degeneration in some muscles a few days before death.

The typical reaction in this disease seems to be a quantitative (not qualitative) diminution to both currents; greater diminution for the faradic than for the galvanic is usually present; almost every writer remarks on the ease with which these patients tolerate strong faradic currents.

Like the tendon reflexes, the electrical reactions are not the same in all muscle groups; they may be normal in upper extremities and diminished in lower extremities and vice versa; the muscles of the face most usually show normal reactions.

Sensory Examination.—It was usually normal; in twelve cases diminished sensation to needle pricks was noted; it was especially marked in six cases (1, 9, 25, 69, 127).

Mental Status.—Mentality was normal in sixty-one cases; in twenty cases mental backwardness was present, and in two, idiocy existed; a small number were noted to be precocious.

Metabolic Observations.—Gittings and Pemberton found that in this disease the creatinin shows a great departure from normal controls, and that there is no marked evidence of disturbance in the calcium metabolism. (The experiments were carried out on the case reported by Griffith.)

Lumbar Puncture.—The spinal fluid was examined in three cases and was normal in all (Skoog, two cases; DeVilla); the blood was examined in two cases and was also normal.

COURSE OF THE DISEASE

In the great majority of the congenital cases, the progress is one of slow but gradual improvement; however, in not a single case was there complete recovery; in the cases in which the symptoms became manifest quite suddenly after an acute illness, improvement was usually more rapid than in the former group of cases. In a small minority of cases (thirteen cases: 133, 107, 108, 109, 85, 43, 44, 36, 41, 26, 5) there was no improvement noted at any time; in these cases there was progressive deterioration up to death. In some of the cases in which there was progressive improvement, there were noted long periods in which the condition was stationary, and then they gradually improved or deteriorated. In a small number of cases, after certain motor accomplishments had been attained, they were lost and regained in the future (in certain instances). The patient of Schüller was able to sit and stand at 10 months, and was no longer able to do either at 12 months; the patient of Haberman could no longer sit up after he had been able to do so; in Case 26 the patient, at 18 months, could creep and later could not; in Case 113, the patient, at 9 months, could sit and stand, and gradually ceased both; in Case 10 the patient sat up at 7 months, and at 11 months had lost this power; the patient of Berti, at 3 years, began to grasp toys and to move the legs somewhat; this it did until it was 5 years old; there was no further improvement for some time, and then suddenly the patient was able to move about and to stand.

PROGNOSIS

The prognosis as to recovery is absolutely bad; there is no record of complete recovery in a single case. Of eighty-four cases, in which

the final outcome was stated, forty-five are known to have died; of these:

Twenty-five died between birth and 6 months of age
Four died between 6 months and 1 year of age
Four died between 1 year and 2 years of age
One died between 2 years and 3 years of age
Three died between 3 years and 4 years of age
Three died between 5 years and 6 years of age
Five, age of death unknown

Of the deaths:

In thirty-two death was due to bronchopneumonia
In five cause of death was unknown
In one death was due to choking fit
In three death was due to convulsions
In one death was due to fever (?)
In one death was due to attack of cyanosis
In one death was due to diphtheria

From these statistics it becomes apparent why there are so few cases reported in older children; of forty-two infants of whom the final outcome was known at time of report, twenty-nine are known to have died before the age of 1 year (a mortality of about 70 per cent.). One cannot understand why it is, in the face of these statistics, that many writers give such a favorable prognosis in this disease.

TREATMENT

In a disease in which there is a natural tendency for a certain amount of improvement to take place, it is hard to judge the effect of treatment; in certain cases there is no improvement brought about by measures which seem to have caused marked improvement in others. I have tried thyroid in every case without the slightest effect; others have reported good results from thyroid and epinephrin; faradism, galvanism, exercise, massage and corrective measure applied to the contracted muscles are indicated. In older children, general tonics, cod liver oil and especially strychnin may be of service.

PATHOLOGY

In studying the pathologic findings we find that the central nervous system was normal in the cases of Baudouin and Lereboullet, Spiller, Brunard, Councilman and Dunn (only very slight changes).

There was remarkable concordance in the pathologic findings of Baudouin, Collier and Holmes, Rothmann, Marburg, DeVilla, Foot, Griffith, Kaumheimer and Concetti; these found pathologic changes in the anterior horn cells, in the fibers which emanate from these cells and from the peripheral nerves, and they have traced the same changes into the muscles and into other organs (thymus and thyroid). In the cases of Baudouin, Collier and Holmes, and Rothmann, the lesions

showed absence of all inflammatory signs, and mostly spoke for a simple arrested development; in the case of Marburg, there was evidence of true destruction (vacuolation, intense sclerosis and fragmentation of the cylinders).

Sclerosis of the thymus was found in the cases of Spiller, Councilman, Rothmann, Baudouin and Pollak, and the thyroid was affected in the cases of Berti, Spiller, Baudouin, Concetti and Pollak.

CEREBRUM

The following writers have found noteworthy pathologic lesions either in the cerebrum or in the nuclei of the cranial nerves. Baudouin found the cells of the nuclei of the sixth and the twelfth cranial nerves in a state of chromatolysis. Collier and Holmes found pathologic changes in the nuclei of the hypoglossal and the ambiguous nerves. Griffith found the brain unusually large, and the cells of the hypoglossal nucleus were diminished in number; the pia was edematous. Kaumheimer found an increase of glia in the cerebrum, medulla and cord; pathologic changes were also found in the cells of the nuclei of the hypoglossal and the ambiguous nerves. Rothman found at the nucleus of the hypoglossal marked development of the blood vessels, the cells were degenerated and there was a diminished number of motor cells in the nuclei; the same was true in the vagus nucleus; in the height of the pyramidal tracts, there was still more marked absence of motor ganglion cells; the cerebellum was small. Berghinz found hypoplasia and microgyria of the cerebrum; the nerve cells of the cerebellum were small. Concetti found all layers of the cerebrum reduced in volume, and the Purkinje cells of the cerebrum were few and altered in shape.

SPINAL CORD

With the exception of those cases in which there were no lesions found in the cord, the findings were fairly uniform; the anterior roots were reduced in size and contained many fibers deficient in myelin; the posterior roots were usually of normal size (except in Rothmann's case); the number of cells in the anterior horns was decreased, and there was an absence of the large ganglion cells (Archangelsky). The cells which were present were of irregular shapes and usually of smaller caliber than normal cells; a number of these cells showed pyknosis or vacuolation.

Changes in the cells of Clarke's columns were found by Rothmann, Archangelsky, Kaumheimer and Marburg; the cord columns occasionally showed deficient myelinization; an increase in the neuroglia of the cord was found by Kaumheimer, Foot, Rothmann and Marburg; the nerve fibers in the cord were diminished in number and lacked myelinization (Archangelsky).

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Preg-nancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Archangelsky and Abrikosoff	1	♀	3½ mo.	++	+	+	+	Swallowing affected	Abolished
Ashby.....	2	♀	8 yr.	++	+	+	+	Swallowing affected	Abolished or weak Feeble
Ausset.....	3	♀	2¾ yr.	++	+	+	+	Abolished
Baudouin.....	4	♀	4 mo.	+	+	+	+	Abolished
Batten.....	5	♀	6 yr.	10th	+	+	+	+	Abolished
	6	♂	6 yr.	3d	+	..	+	+	Abolished
	7	♂	7 yr.	9th	+	+	+	..	Face expres-sionless	Abolished
	8	♂	6 yr.	+	+	+	Present
Beling.....	9	♂	3½ yr.	3d	+	+	+	+
Beavor.....	10	♀	20 mo.	++	+	+	Abolished
Bergblaz.....	11*
Bernhard.....	12	♂	9 mo., prema-ture	++	+	..	+
Berti.....	13	♀	5 yr.	++	+	Feeble
	14	♂	3 days	+	+	+	+	Abolished
Bienfalt.....	15	♂	12 mo.	+	+	+	+	Feeble
Bing.....	16	♂	3½ yr.	++	+	+	Abolished
Bunard.....	17	♀	2 yr.	+	+	+	Knee jerks present
Careupino.....	18	♀	3½ mo.	+	+	+	+	Diminished or abolished
Cattaneo.....	19	♀	4 mo.	+	+	+	+	Abolished
Charles.....	20	♂	6 yr.	1st	++	+	+	Knee jerks present
Chéné.....	21	♀	6 mo.	+	+	+	+	Abolished
Collier and Wilson	22	♂	4¼ yr.	2d	++	+	Mastication affected; face affected	Abolished
	23	♂	7 yr.	1st	+	++	+	..	Facial muscles weak; unable to close eyes completely	Abolished
	24	♂	5¼ yr.	5th	++	+	Abolished or feeble
	25	♀	1¾ yr.	1st	++	Abolished
Collier and Holmes	26	♂	3½ yr.	5th	+	+	+	+	Abolished
Collier.....	27	♂	5 yr.	++	Feeble
Comby.....	28	♂	8 yr.	+	+	+	+	Abolished
	29	♂	4 mo.	++	+	+	+	Difficulty in swallowing	Abolished

* No clinical details.

—THE LITERATURE

Electrical Reactions	Contractures	Mentality	Progress	Cause of Death	Necropsy Biopsy	Remarks
No response to faradic	Equinovarus; arms	Normal	Died	Pneumonia	+	Chest deformed; abdominal breathing; diminished pain sensation; double wrist drop
Normal	Backward	Improvement	Could take a few steps at 4 years
Normal	Normal	Improvement	Abdominal breathing
No response to faradic	Normal	Improvement	Pneumonia	+	
.....	Knees, hips	Normal	No improvement; died	?		
Diminished to faradic; absent to galvanic	Normal	Died	?		
Diminished to faradic	Legs	Normal				
Diminished to faradic	Improvement	Marked lordosis
.....	Knees	Normal	Pain sensation diminished
Persistent to violent current; diminished	Normal	Improvement	Onset at 12 months after a bronchitis; later tendon reflexes returned
.....	+	Necropsy
No response to faradic; diminished galvanic	Premature birth; kyphoscoliosis
Diminished faradic	Normal	Improvement	Hard edema of legs
Diminished faradic or absent	Improvement	Abdominal breathing
.....	Backward	Improvement	
Faradic normal; galvanic diminished	Improvement	
Electric reactions not diminished	Idiot	Improvement	Athetosis of hands; normal at birth; convulsions at 2 months; syphilitic keratitis
Diminished or absent	Improvement; died	Pneumonia	Reaction of degeneration in muscles before death
Diminished to both	Normal	Kyphosis; abdominal breathing; hard edema of feet; spina bifida
Diminished faradic	Began to walk at 2 years; convulsion at 1 year; kyphosis; flat feet, long and narrow
Diminished to both	Normal	Improvement	First noticed at end of second month
Normal faradic	Hip, knee	Normal	Improvement	Legs cold, blue; kyphosis; flat feet
Diminished to faradic	Legs	Normal	Improvement	Later could walk a little
Diminished to faradic, normal to galvanic	Thighs, feet	Normal	Improvement; died at 7 years	Pneumonia	+	Kyphosis; onset at 6 months
Diminished but present	Hips	Fair	Improvement	Well until 12 months; onset followed bronchitis; diminished sensation to pain
Diminished faradic	Thighs, calves	Normal	No improvement	At 18 months could creep; later could not; kyphosis
Diminished faradic	Improvement	+	
.....	Normal	Kyphosis; could not walk
Diminished excitability	Normal	Improvement	Onset at 1 month after diarrhea; kyphosis

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Pregnancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Concetti.....	30	♂	10 wk., premature	7th	+	+	Facial immobility	Abolished
	31	♂	7 mo.	2d	+	+	+	+	Abolished
	32	♀	8 mo.	+	+	+	+	Voice feeble; automatic movements of mastication	Abolished
	33	♀	1st	+	+	+	+	Extremely fat
	34†	♂	2 mo.	2d	+	+	+	+	Face apathetic
	35	♂	6 mo.	++	+	Adipose tissue abundant	Abolished
	36	♀	4½ mo.	+	+	+	+
	37	♀	3 yr.	++	+	Father alcoholic; adipose tissue abundant	Feeble
	38	♀	53 days	++	+	+	+	Abolished
Ooombs.....	39	♀	10 yr.	+	++	+	..	Orbicularis palpebrarum; flat, toneless	Present in lower; absent in upper
Cotteril.....	40	♀	2½ yr.	4th	++	+	+	+	Could not suck; face vacant; mouth open; eyelids droop	Abolished
Councilman and Dunn	41	♂	6 mo.	2d	+	++	+	+	Swallowing difficult	Abolished
Courtney and Eaton	42	♂	5½ yr.	++	+	+	+	Abolished
Dunn.....	43	♂	5 mo.	2d	+	+	+	+	Nursing difficult	Abolished
	44	♀	5 mo.	2d	+	+	+	+	Lost power of sucking; could not swallow	Abolished
Duthoit.....	45	♀	2 yr.	+	+	+	+	Face atonic	Abolished
Feer.....	46	♀	4½ mo.	++	+	+	+	Abolished
Fletcher.....	47	♂	3 yr.	4th	+	+	+	+	Face expressionless	Feeble
Foot.....	48	♂	3½ mo.	8th	+	+	Cry feeble	Feeble
Faber.....	49	♂	29 mo.	3d	+	..	+	+	Pronounced
	50	♂	8 wk.	2d	++	+
	51	♂	30 mo.	2d	++	+	+	+	Expression inert skull peculiar in shape	Abolished
Fievez.....	52†									

† Brother of No. 33.

‡ Details not obtainable.

—THE LITERATURE—(Continued)

Electrical Reactions	Contractions	Mentality	Progress	Cause of Death	Neeropsy Biopsy	Remarks
Diminished	Normal	Improvement; died	Pneumonia	Kyphosis; abdominal breathing; arms supinated
.....	Backward	Improvement; died	Pneumonia	Edema of legs (hard); kyphosis; testes undescended; penis rudimentary
.....	Backward	Improvement; died	Mongolian facies; general pseudo-edema; adiposity
.....	Died at 3 months	Pneumonia	Patient not seen; history from parents
.....	Improvement; died at 5 months	Pneumonia	Hard edema of calves, thighs and forearms; abdominal breathing
.....	Backward	Lordosis
.....	Died; no improvement	Bronchial pneumonia	First noticed at 2 months; signs of hypothyroidism; umbilical hernia; firm edema; constipation
Diminished to faradic and galvanic	Backward	Improvement	Kyphosis; constipation; walked at 3 years with support
Diminished to faradic and galvanic	Died at 2 months	Pneumonia	Arms abducted and supinated; kyphosis; thorax deformed; abdominal breathing
Diminished to faradic and galvanic	Improvement	Began to walk at 2½ years; onset at 12 months
Slightly dim to faradic and to galvanic	Sternocleidomastoid; left hand; club foot; equinovarus	Backward	Constipated; incontinence of urine and feces; umbilical hernia; winged scapulae; pectus excavatum; thumbs dislocated; right hip dislocated; athetoid movements
.....	Normal	Improvement and later worse; died	Choking fit	+	Drop wrist onset at 3 weeks; chest deformed; abdominal breathing
Normal	Normal	Improvement	Speech defective; premature; reflexes returned; drooled; walked
.....	Normal	Progressively worse; died	Pneumonia	Abdominal breathing
.....	Normal	Worse; died	Pneumonia	Abdominal breathing; chest deformed
Diminished galvanic in legs; normal in arms; diminished faradic	Normal	Improvement	Abdominal breathing; kyphosis; athetoid movements
Diminished to faradic and galvanic	Equinovarus	Normal	Slow improvement	Rotatory movement of head; hands pronated; abdominal breathing
Diminished to faradic	Knee	Normal	Wassermann negative
Diminished to faradic and galvanic	Died	Pneumonia	Thumbs dislocated; first and second children born paralyzed and died at 6 months and 9 weeks, respectively
Diminished to faradic and galvanic	Backward	Convulsions in first week; no paralysis until walking time; tendency to adduct thighs; kyphosis
Faradic absent; galvanic normal	Cesarean section; Wassermann negative; hands pronated; arms abducted
Diminished to faradic and galvanic	Normal	No improvement	Onset at 3 months; funnel chest; abdominal breathing; kyphosis; index finger hyperextended; drop wrist; Babinski reflex present

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Preg- nancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Fearnside.....	53	♂	3½ yr.	+	+	+	+	Muscles of face and jaw feeble; face flat	Abolished
Gastonguay....	54	♀	3¾ yr.	3d	+	+	+	+	Abolished
Gatti.....	55	♂	3 yr.	++	+	Normal
Gordon.....	56§	♀	2 yr.	+	+	+	+	Optic nerves atrophic	Abolished
	57	♀	3 yr.	+	+	+	+	Feeble
Griffith.....	58	♂	15 mo	+	+	+	+	Abolished
Guinon and Gauducheau	59	?	?	+	+	+	+	Ptosis; nystag- mus; strabismus; deafness	Abolished
Guillemot.....	60	?	18 mo	+	+	+	+
Gött.....	61	♂	2½ yr.	+	+	+	+	Abolished
Haberman.....	62	♀	3½ yr.	++	Abolished
	63	..	4 mo.	+	+	+	+	Abolished
	64	♀	18 mo.	+	+	+	+	Converging strabismus	Abolished
Hertz and Johnson	65	♂	3½ yr.	+	+	+	+	Abolished
Hummel.....	66	♂	3 yr.	++	+	+	+	Abolished
Hartenberg.....	67	♀	50 yr.	++	Feeble
Jovane.....	68	♂	3 mo.	+	+	Abolished
Kaumheimer...	69	♀	3¾ mo.	+	++	+	+	Abolished
Keersmaker. ...	70	♂	7th	+	+ Atle- toid move- ments	+	+	Abolished; Babinski re- flex present
Kundt.....	71	♀	18 mo	+	Abolished or diminished
Koch.....	72	?	15 mo.	2d	+	++	++	+	Nystagmus	Feeble
Lafler.....	73	♀	8 yr.	1st	+	+	Face immobile; drooping of eyelids	Present
Leclerc.....	74	♀	4 yr.	4th	+	+	+	+	Abolished
Lereboullet and Baudouin	75	♂	11 mo.	2d	+	+	++	+++	Diminished
Lungenbühl....	76	♀	5 mo.	++	+	+	+	Abolished
Marburg.	77	♂	3 mo.	7th	+	++	+	+	Abolished
	78	♀	6 yr	+	+	+	Abolished

§ Colored.

—THE LITERATURE—(Continued)

Electrical Reactions	Contractures	Mentality	Progress	Cause of Death	Neeropsy Biopsy	Remarks
Normal	Adductors of thigh	Backward	First noticed at 6 weeks; drooled; knee jerks returned; kyphosis; Wassermann negative
.....	Premature; genu recurvatum
Normal	Improvement	Flat feet
Diminished to faradic and galvanic	Equinovarus	Backward	Improvement	Skull peculiar; Wassermann positive
Diminished to faradic and galvanic	Fair	Improvement	Wassermann negative
Absence of all faradic and galvanic response	Slight contracture	Improvement; died	Pneumonia	+	Abdominal breathing
Normal	Transient hypertonicity; exaggerated extension of head; subluxation of inferior maxilla
.....	Improvement	Reported in discussion of Comby's case
Diminished to faradic and galvanic; partial reaction of degeneration	Normal	No improvement and no worse; died	Pneumonia	+	Both index fingers overextended; fibrillary twitches in hands
Total loss in some muscles, diminished in others	Normal	Died	Unknown	Walked with support
Diminished to both	Normal	Lordosis
Diminished to both	Normal	First noticed in sixth month; could not hold head up, which it could before; constipation; abdominal breathing
.....	Normal	Improvement	Scoliosis
Diminished to both	Normal	Kyphosis
Normal	Scoliosis; married; mother of a son; walked
Diminished to faradic; absent to galvanic	Died at 5 months	Pneumonia	Abdominal breathing
Diminished to both	Arms	Normal	Died	Pneumonia	+	Arms elevated; flexed; pronated; flat feet; chest deformed; sensation diminished; Wassermann negative
Diminished to both	Improvement	Kyphosis; abdominal breathing; marked vasomotor reactions; Wassermann negative
Normal, only slightly diminished	Normal	Improvement	Röntgen ray of bones normal
Diminished to both	Normal	Onset at 6 months
Greatly diminished to faradic	Normal	Walked at 14 months; lordosis
Diminished	Backward	Slow improvement	Onset at 7 weeks after pneumonia; hard edema of legs
.....	Died	Convulsions	Convulsive fits; hard edema
No response to faradic and galvanic?	Improvement	Abdominal breathing
.....	Arms	Normal	Died	Pneumonia	+	Onset at 6 weeks; funnel-shaped sternum
Diminished to both	Thighs; legs; equinus elbows	Normal	+	Walked since age of 5 years, erect position

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Preg- nancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Mensi.....	79	♀	12 days	++
	80	♂	4 days	+	+
	81	♂	2 days	++	+	+
	82	♀	1½ mo.	+	++	Absent
	83	♀	At birth	+	++	+	+	Plantar pa- tella present
Moussous and Oarles	84	♀	4½ yr.	+++	++	Face inert	Abolished
Muggla.....	85	♀	4 yr.	++	+	Normal (feeble)
Mettenheimer, Götzky and Welhe	86	?	8 mo.	+	+
	87	?	5 mo.	+	+	+	+
Naish.....	88	♂	4½ yr.	+	++	+	+	Just present
Ollari.....	89	♀	70 days	+	+	+	+	Abolished
Openshaw.....	90	♂	7½ yr.	+	+	..	+	Abolished
Orblson.....	91	♀	4 yr.	3d	+	+	+	+	Could not see well or hear acutely; strabismus	Present
Oppenheim.....	92†	+	+	+	+	Abolished
	93	♀	19 mo.	+	+	Abolished
	94	♂	12 yr.	+	+	+	Abdominal reflex absent; feeble
Pollak.....	95	♂	4 mo.	+	+	+	+	Weak voice; face muscles; swallow- ing affected; hypoglossal nerve involved	Abolished
Pelz.....	96	..	1¼ yr.
Princeteau.....	97#									
Purser.....	98	♂	2¼ yr.	++	+	+	+	Nystagmus; facial muscles somewhat affected	Abolished
Reiner.....	99(1)	♀	3 yr.	+	+	+	+	Abolished; Babinski re- flex positive
	99(2)	♂	11 mo.	+	+	+	+	Diminished
Reyher and Helmholtz	100
Rosenberg.....	101	♂	2½ yr.	++	Abolished
Rothmann.....	102	?	5 mo.	1st	++	+	Abolished
Rocher.....	103**									
Rad.....	104††									
Rietschel.....	105††	?	4 yr.
Reuben.....	106	♀	5½ mo. Prema- ture	1st	+	+	+	+	Difficulty in swal- lowing; face im- mobile; voice weak	Abolished
	107§§	♀	3 mo.	1st	+	+	+	+	Difficulty in swal- lowing	Abolished
	108§§	♀	6 mo.	2d	+	+	+	+	Difficulty in swal- lowing; sensation diminished; face immobile; feeble voice	Abolished
	109§§	♀	10 wk.	3d	+	+	+	+	Difficulty in swal- lowing; sensation diminished; fee- ble voice	Abolished

† Four cases.

In discussing the case of Moussous, he said he had seen a case. No details were obtainable.

** In discussing case of Moussous, stated he had seen a case; no details.

†† Festschrift des Cnappschen Kinderspitals, Neuremberg, 1914. No details were obtainable.

‡‡ No details.

§§ Sisters.

Electrical Reactions	Contractions	Mentality	Progress	Cause of Death	Necropsy Biopsy	Remarks
.....	Slight contraction	Died	Pneumonia	+	Flexure of forearm, arms and fingers
.....	Died 27 days	Pneumonia	+	Edema of feet and legs
.....	Died 2 months	Pneumonia	+	
.....	Died	Pneumonia	+	Edema of arms and legs
.....	Died 3 weeks	Pneumonia	+	Hemorrhage into suprarenal capsules
Diminished to both Normal	Backward	Could not walk or stand
.....	No improvement Died	Pneumonia	+	
Partial reaction of degeneration in lower extremities	Died	Pertussis and pneumonia	+	
Diminished to both	Normal	Walked since age of 4 years; flat feet
Diminished to faradic	Normal	Improvement	
Diminished to faradic and normal galvanic or	Hips	Normal	+	Onset at 18 months after measles; began to walk at 2½ years
Diminished to faradic	Hamstring	Backward	Normal up to 6 months; convulsions at 1 year; hands and feet long
Diminished or absent	Normal	Improvement	
Absent except in peroneus	Normal	Improvement	
Diminished	Knee; back; biceps	Normal	Stationary; later worse	Could not walk
No reaction to galvanic or faradic	Improvement; died	Bronchitis	+	Kyphosis; abdominal breathing; constipation; necropsy not reported
.....	Idiot	
Absent	Normal	Improvement	
Diminished to both	Normal	Improvement	One of twins
Diminished	Normal	Improvement	
.....	Died	?	?	+	
Absent or diminished	Hamstrings	Normal	Improvement	Sat up at 7 months; first noticed at 11 months
Absent or diminished	Normal	Died at 5 months	+	Reaction of degeneration in some muscles
.....	Improvement	
Absence of faradic response; galvanic diminished	Normal	Improvement	Abdominal breathing; Wassermann negative; normal roentgen-ray development
.....	Normal	No improvement; died	Pneumonia 4 months	Wassermann of mother negative; abdominal breathing
Diminished to both	Sterno-cleido-mastoid	Normal	Improvement; died	Pneumonia 10 months	Drop wrist; chest deformed; abdominal breathing; roentgen ray normal
Diminished to both	Normal	No improvement; died	Pneumonia 4 months	Chest deformed; abdominal breathing

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Pregnancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Reuben.....	110	♀	8 mo.	2d	+	+	+	+	Strabismus; amaurosis	Abolished or feeble
	111	♂	14 mo.	3d	+	+	+	+	Abolished
Schippers.....	112	♂	2 yr.	++	Babinski positive
Schüller.....	113	♂	19 mo.	++	+	..	+	Abolished or feeble
Schlivek.....	114	♀	2¼ yr.	1st	+	++	Normal
Skoog.....	115	♂	6 yr.	3d	+	+	+	+	Muscle of jaw and tongue affected; jaw drooped	Abolished
	116 ^{¶¶}	♂	4 yr.	4th	+	+	+	+	Abolished
	117	♀	22 mo.	+	+	+	+	Face affected	Abolished
Snow.....	118	♂	2¾ yr.	5th	++	Tremor of hands	Abolished; Babinski present
Sorgente.....	119	♂	27 days	+	+	Abolished
	120 ^{¶¶}	♀	5 days	+	+
Simonini.....	121	♀	10 mo.	++	+	+	+	Feeble
Silvestri.....	122	♂	45 days	+	+	+	+	Abolished
Spiller.....	123	♂	22 mo.	+	++	Amaurosis; strabismus; could not swallow	Absent
Strauch.....	124	♀	6 mo.	2d	+	+	+	+	Cry feeble; face affected	Abolished
Sutherland.....	125	♂	2 yr.	+	+	+	+	nystagmus	Abolished
Thompson.....	126	♀	14 mo.	3d	+	+	+	+	Present
Thorspecken....	127	♀	4½ yr.	++	+	+++	+	Absent in lower, present in upper
Tobler.....	128	♂	1¾ yr.	1st	+	+	+	+	Facial muscles inactive	Abolished
Variot and Chatelin	129	♀	3½ yr.	++	+	+	Abolished
Variot and DeVillers	130	♀	6 mo.	+	+	+	+
de Villa.....	131	♂	3 yr.	+	+	+	+	Abolished
	132	♀	3 yr.	2d	+	+	+	+	Abolished
Wynter.....	133	..	15 mo.	+	+	+	+	?
Zahorsky.....	134	♂	2½ yr.	+	+	+	+	Diminished
Zappert.....	135	♂	6½ mo.	++	+	+	+	Abolished
Wimmer.....	136	♂	16 mo.	+	+	+	+	Could not nurse	Abolished

¶¶ Brother of No. 115?

¶ Sister of No. 119.

—THE LITERATURE—(Continued)

Electrical Reactions	Contractions	Mentality	Progress	Cause of Death	Neeropsy Biopsy	Remarks
No response to faradic; diminished to galvanic	?	Improvement	Wassermann of mother negative; chest deformed; funnel chest
.....	Normal	Improvement; died at 14 months	Pneumonia	
Diminished to both	Improvement	Athetoid movements of fingers; marked dermatographia
Diminished to both	At 9 months could sit and stand; gradually ceased both
Diminished to both	Normal	Improvement	Arms in position of Erb's paralysis
Diminished to both	Normal	Improvement	+	Wassermann negative
Diminished to both	Normal	Improvement	+	Wassermann negative
Absent or diminished to both	Normal	Improvement	+	
Normal or diminished	Backward	Improvement	Onset at 2 months after meningitis ? kyphosis; walked at 3 years
Absent to both	Improvement; died at 1 month	Bronchitis and convulsions	Abdominal breathing
.....	Died at 15 days	Convulsions	
Diminished	Abdominal breathing
Faradic absent	Marked improvement in 4 months	Treated with suprarenal extract
Normal in legs	Improvement; died	Fever ?	+	First noted at 5 months
Absent	Normal	Improvement; died	Attack of cyanosis	+	Abdominal breathing; constipation; edema of feet
.....	Backward	
Diminished to both	Normal	Great improvement	First noticed at 3 months
Diminished to both; reaction of degeneration in some muscles	Club foot	Normal	Improvement	Sensation diminished; legs cyanotic and cold; bone of legs atrophic; flat feet; Wassermann negative; chest deformed
Diminished or absent	Normal	Improvement; died	Diphtheria	Kyphosis
Diminished to both	Hip	Normal	Symptoms noted at 6 months
.....	Died	Pneumonia at 6 months	+	Kyphosis; no report of neeropsy
Diminished to both	Died	Pneumonia	Abdominal breathing; Wassermann negative; lumbar puncture
Diminished; certain contractions slow	Improvement	Normal
No response to faradic	Normal	Grew worse	Child could walk
No response to electricity ?	Talipes equinus	
Diminished to both; beginning reaction of degeneration	Talipes varus	Normal	Progressive	Arms elevated and flexed at elbows; supination of arms; abdominal breathing
						Feet cyanotic; atrophy marked in this case

The nerve roots were small and very slender. Councilman found slight degeneration in the myelin of the posterior columns, anterior and posterior nerve roots and in the spinal ganglia. DeVilla found slight rarefaction of the pyramidal bundles. Foot noted marked gliosis in the anterior horns. Gliosis was found by Kaumheimer, Marburg, Rothmann and Foot (especially in the anterior horns).

MUSCLES

The gross appearance of the muscles has been compared by Foot to that of raw pork; the muscle is usually thin, pale, doughy and flabby; the amount of fat around the muscle fibers is in most cases excessive; slight changes in the diaphragm have been found by Councilman and Foot; the most conspicuous finding is the disproportion in the size of the fibers; the small fibers predominate in the majority of cases; some fibers are composed of 1 or 2 fibrils, others are of normal size. In certain cases large hypertrophied fibers were found (Archangelsky, Baudouin, Collier and Holmes, Concetti, Griffith, Kaumheimer, Lereboullet, Marburg, Mettenheimer, Reyher and Helmholtz); in a few the hypertrophy is only apparent on account of the presence of the very small fibers.

The cross striations are usually well preserved; they were indistinct or absent in the following cases: Mensi, Griffith, Kaumheimer, Lereboullet, Reyher, Skoog and Spiller. The sarcolemma nuclei are increased in number; in many undoubtedly this increase is due to an apparent disproportion in size of fibers and nuclei (fibers are small and nuclei are of normal size).

The amount of perimuscular fat is usually increased, as is also the connective tissue; in the following cases no increase was noted: Archangelsky and DeVilla.

No hypertrophic fibers were found in cases of Councilman, DeVilla, Mensi, Bing, Rothmann, Skoog (Table 2).

PERIPHERAL NERVES

The peripheral nerves show deficient myelinization of their fibers, and increase of connective tissue. In certain cases the nerves appear small; in many, the nerve endings could not be demonstrated in the muscles. Empty neurilemma were found by Archangelsky, though all signs of degeneration were lacking; in the case of Griffith, the nerves were very much degenerated; the intramuscular fibers showed considerable degeneration and the medullary substance was broken down into small balls. Kaumheimer also found signs of severe degeneration in the nerves; the number of fibers was diminished, but no axis cylinder was found without a medullary sheath; the number of the nuclei of Schwann was increased; Marburg also found signs of degeneration

TABLE 2.—SUMMARY OF MUSCLE FINDINGS

	Normal Fibers	Small Fibers	Hyper- trophied Fibers	Fat In- creased	Con- nective Tissue Increased	Nuclei Increased	Trans- verse Stria- tions Pre- served	Longi- tudinal Stria- tions Pre- served
Archangelsky.....	++	+++	+	—	—	—	+	+
Baudouin.....	+	+++	++	+	+	+	+	+
Bing.....	+++	+ ?		
Collier.....	+	+++	++	++	++	++	+	+
Collier.....	+	+++	++	+++	+++	+++	+	+
Counellman.....	++	++ ¹	++	++	+	+
DeVila.....	+	+++	—	—	—	+	+
Concetti.....	+	+++	+	—	—	+	+
Foot.....	+	+++	+	+	+	+
Griffith.....	+	+++	+	+++	+++	+++	+	—
Kaumbenner....	++	++	++	++	+	—
Lereboullet.....	+	++	++	++	—	+
Marburg.....	++	+++	+	++	++	++	+	+
Marburg.....	+++	+	++				
Mettenheimer....	++	++					
Reyher.....	+	+	+	+	+	+	—	+
Rothmann.....	++	++	+	+	+		
Skoog.....	+	+++	++	++	++	—	+
Skoog.....	+	+++	++	++	++		
Spiller.....	++	+++	++	++	++	+	—
Mensl.....	+++	—	—
Openshaw.....	+	+++	—	

and sclerosis; there were fewer fibers than normal, and those present were deficient in myelin; in many the entrance of nerves into muscle fibers can be seen, but the end plates cannot be demonstrated; the nerves in the case of Strauch showed marked, but not very profound degenerative changes; myelin sheaths were well preserved, but here and there it was thinned out; occasional breaks in the myelin sheath were present; the interstitial connective tissue was increased. Spiller and Lereboullet found nerves normal.

BLOOD VESSELS

The blood vessels were thickened in a number of cases (Skoog, Rothmann, Griffith, Marburg, Collier). The thickening is due to an increase of connective tissue.

OTHER FINDINGS

Small round cell infiltration was noted by Rothmann, Marburg, Collier and Holmes, and by Foot. The significance of these cells is hard to estimate; a few have looked on them as evidence of inflammatory changes. Rigor mortis was absent in all cases.

SUMMARY

To summarize, we may say that in the seven cases we may find pathologic changes in all the skeletal muscles and in the whole cerebrospinal system (from the brain to the end plates); the severity of the disease depends on the extent of muscular involvement and date of onset of disease; the more general is the distribution of muscular involvement, and the earlier the symptoms became manifest, the greater are the pathologic changes in the nervous system.

Pathologic changes have been found in the cerebrum, cerebellum, cord, peripheral nerves and muscles. The changes in the cerebrum consist in a diminution of the number of motor cells of the cortex and the cranial nuclei; the cord may be diminished in caliber; the motor cells of the ventral horns are reduced in number, and those present are of irregular shape and of smaller size; the anterior horns and roots are smaller than normal; the muscles are partially replaced by fat, and contain a considerable amount of connective tissue; some muscle fibers are normal; most are very small; many are hypertrophic; striations are well preserved in most cases; the sarcolemma nuclei are apparently increased in number; the peripheral nerves are reduced in size, contain fewer fibers and the fibers show deficient myelinization; the end plates can be demonstrated in only few cases; marked thickening of the adventitia of the blood vessels of the cerebrospinal axis was noted in a few cases (periarteritis); in a few cases changes (sclerosis) were noted in the thymus and the thyroid.

The presence of certain contractures, convulsions, athetosis and exaggerated reflexes point in certain cases to the involvement of the corticospinal tract.

PATHOGENESIS

Oppenheim believed this disease is due to an arrested development of the muscle tissue, but he did not exclude the possibility that the primary seat of the disease may be in the anterior horn cells.

Spiller also believed that this disease is due to an arrested development of the muscular tissue. Allen Smith, on the strength of finding a much sclerosed thymus in Spiller's case, believed that the whole clinical picture is due to the thymic changes.

Baudouin believed that arrested development alone could not explain all the pathologic findings in these cases; thus the proliferation of connective tissue, the enormous hypertrophy of certain fibers, the multiplication of nuclei of the sarcoplasm signify more than simple

arrest. He believes that dysfunction of the thyroid is the exciting cause that brings about this condition. Berti also expressed the view that this disease has something in common with myxedema. Concetti, above others, is of the opinion that the organs of internal secretion (especially the thyroid) are important etiologic factors in the production of this disease; he frequently observed improvement in these cases from the administration of thyroid extract; the underlying cause, however, he thought was to be explained by the assumption of abiotrophy of the whole neuromuscular apparatus. (Skoog was also of the same opinion.)

Marburg, on the strength of the necropsy findings in his case, did not believe that the disease is due to an arrested development. The findings in his case led him to the belief that he was dealing with a terminal process which had its inception in fetal life; the pathologic lesions in his case did not resemble those found in fetal life (arrested development), nor those seen in spinal (progressive) atrophy. It appeared to him that the process in his case was one of inflammation with small round cell infiltration, such as was noted by Rothmann in the nucleus of the hypoglossal nerve; he was, therefore, inclined to the conclusion that the disease was due to an acute fetal poliomyelitis.

Baudouin believed that the primary seat of this disease is in the cord; he believed that arrested development of the gray matter of the cord and the nerves precedes secondary atrophy of the muscles.

Bernhardt adduced some evidence to show that this disease may be due to a multiple polyneuritis.

Rothmann and others (Beevor and Wimmer); from a study of the pathologic lesions in their cases, believed amyotonia congenita to be a subgroup of Werdnig-Hoffman's type of paralysis. Bing, on the contrary, thought that the disease is due to an arrested development of the spinocerebellar tracts. Kaumheimer was of the opinion that this disease is due to a toxemia of unknown origin, or that it is of endogenous origin.

To us it appears that the pathogenesis of this disease is to be sought in a primary abiotrophy of the musculature and a secondary failure of proper development of the whole nervous system (cerebrospinal axis and peripheral nerves) brought about by deficient natural stimulation to its growth by the abiotrophic musculature.

When the heart is stilled life ends almost instantly. Besides this general life, the termination of which involves that of every part of the body, many of these parts have their own vitality; some of them may slowly die, while the life of all the rest goes on without impairment; when the failure is early, it is often due to a defect in vitality, a defect which seems to be inherent, the tendency thereto is born; to this degeneration or decay, in consequence of a defect of vital endurance, Gowers has applied the term "abiotrophy."

TABLE 3.—SUMMARY OF PATHOLOGIC FINDINGS

Author	Cerebrum, Cerebellum, Medulla, Pons	Spinal Cord	Muscles	Peripheral Nerves
Archangelsky and Abrikosoff 7 months	Normal	Anterior roots small; posterior normal; complete absence of large ganglion cells of anterior horns and of Clark's columns; nerve fibers in cord diminished in number and lacking myelin; in the lateral anterior horns, myelinization incomplete and empty neurilemma	Muscles are thin, pale, flabby; no increase of nuclei; no increase of connective tissue; no increase of fat; fibers small, few, hypertrophied; striations distinct.	Nerve endings could not be demonstrated; all nerve cells appeared small; neurilemma empty; all degenerative signs lacking; many fibers not myelinated
2. Baudouin 4 months	Cells of 6th and 12th nerves were in a state of chromatolysis	At level of 8th cervical segment anterior horns were diminished in volume; no evidence of neuron phagocytosis; anterior nerve roots small; sheaths widely spaced; myelinization delayed	Connective tissue sheaths numerous and thickened; masses of small fibers; also very large fibers; nuclei increased in number; striations normal; no degeneration.	No fragmentation of the myelin; number of nerves not yet myelinated
3. Brunard	Doubtful case; no macroscopic lesions found	Nothing said about muscles, except a little sclerosed.	Histologic study promised but not reported; nothing abnormal found macroscopically
4. Collier and Holmes 7 years	Nuclei of hypoglossal and ambiguous nerves showed pathologic changes	Unmistakable pathologic changes in the ventral horns; the large cells were reduced in number; those present small; Clark's column normal; anterior roots very slender	Remarkably pale; infiltrated by fat; few normal fibers; most prominent change in extreme smallness of fibers; proliferation of sarcolenemia nuclei; many enormous fibers present; increase of connective and fat tissue; blood vessels thickened; striations very distinct.	Nerve fibers rather far apart; myelin sheaths rather poorly developed; roots slender
5. Collier and Holmes (dropsy)	Macroscopically, pale and very much infiltrated with fat; many fibers were extremely small; striation well preserved; marked proliferation of nuclei; enormous fibers present; connective tissue greatly increased; notable amount of loose fat tissue
6. Councilman and Dun, 7½ months	Normal	Slight degeneration in the myelin of the posterior columns; also in anterior and posterior nerve roots and in spinal ganglia; sections of the cord showed very slight evidence of change; no diminution in the number of cells in the anterior columns; neuroglia normal	Muscles thin, color and consistency normal; infiltrated with fat; normal fibers and very small muscle fibers; nuclei increased? connective tissue increased; striations normal in most fibers; no fatty degeneration; diaphragm slightly involved	No change in the nerves; number of nerves in the muscles was diminished; nerves in the muscle tissue were found, which showed evident degeneration; a few peripheral nerves lacked myelin; no nerve endings were found in the affected muscles
7. DeVilla	Deficiency in the number of anterior horn cells; slight rarefaction of pyramidal bundles; a few fibers without sheaths	Muscles pale; fibers small; no increase of nuclei; no increase of connective or fat tissue.
8. Foot, 3½ months	Changes in the formatio reticularis and substantia reticularis	Anterior horns were the seat of pathologic lesion; cells were reduced in number and size; some showed vacuolar degeneration and acute swelling; horns shrunken in size; white matter pale, except columns of Goll and Burdack; many small cells resembling the posterior horn cells were present; marked gliosis in anterior horns	Marked differences in size of muscle fibers; most very slender; fat and connective tissue increased; nuclei of normal appearance; muscle pale like "raw pork"; diaphragm slightly involved; striations preserved; fatty changes in some fibers, and others were hyaloid	Marked decrease in medullary sheaths; smaller muscle fibers seemed to be without innervation

TABLE 3.—SUMMARY OF PATHOLOGIC FINDINGS—(Continued)

Author	Cerebrum, Cerebellum, Medulla, Pons	Spinal Cord	Muscles	Peripheral Nerves
9. Griffith, 25 months	Brain unusually large; cells of hypoglossal nucleus diminished in number; pia edematous	Spinal cord membranes edematous; anterior roots small; cells in the anterior horns much diminished in number; Clark's column not affected; anterior roots much degenerated	Great atrophy of fibers; transverse striation preserved, but not longitudinal; atrophy not general; a few very large muscle fibers found; number of nuclei increased; connective tissue fat greatly increased; formation of fat within the muscle fibers was observed only in this case	Very much degenerated; intramuscular fibers showed considerable degeneration; medullary substance broken into small balls
10. Bing (biopsy)	Muscle was normal in all respects except perhaps there was an increase in the number of nuclei
11. Kaumheimer	Increase of glia in cerebrum, medulla and cord; pathologic changes in cells of nuclei of ambiguus and hypoglossal nerves	Gliosis; pathologic changes in anterior horn cells and in cells of Clark's column; slight signs of degeneration in the anterior nerve roots; anterior roots small; cells of anterior horns small, few, pyknotic, degenerated fibers in tracts but did not lack myelin	Manifold symptoms of degeneration; atrophic and hypertrophic fibers, vacuolation, nuclear increase and increase of connective tissue; transverse striations distinct, except in hypertrophic fibers	Signs of severe degeneration; number of fibers diminished, but no axillary cylinders without medullary sheath found; nuclei increased (Schwann)
12. Lereboullet and Baudouin, 15 months	Brain normal	Cord normal; no diminution in size or number of the cells in the anterior horns	Muscle lesions were marked; fibers were of irregular size; transverse striations absent; longitudinal present; nuclei increased; some fibers small; some very large; connective tissue increased
13. Marburg, 3 months	Posterior roots normal; axonal degeneration only in isolated instances; increase in glia nuclei and fibers; increased number of bloodvessels; degeneration of anterior horn cells; deficient myelinization; increase of connective tissue and glia in cord	In addition to normal fibers were found very thin fibers with many nuclei; a few hypertrophic fibers; fat and connective tissue was increased; transverse striation distinct, also longitudinal; nuclei apparently increased	Signs of degeneration and sclerosis; few fibers; these were deficient in myelin
14. Marburg (biopsy)	Occasional hypertrophic fibers found; fairly large amount of fat near normal muscle fibers; no atrophic fibers found
15. Mettenheimer	Recent disease of ganglion cells, atrophy and absence of anterior horn cells	Muscle fibers were atrophic and others were hypertrophic
16. Mettenheimer	Severe degenerative signs in the anterior horn cells of the entire cord
17. Reyher and Helmholtz (biopsy)	In proximity to normal muscle fibers are found either little or much altered fibers. transverse striation lacking; difference in diameters of muscle fibers was especially marked; nuclei interstitial connective tissue and fat increased
18. Pollock	Necropsy performed but not reported	Thymus enlarged; thyroid large

TABLE 3.—SUMMARY OF PATHOLOGIC FINDINGS—(Continued)

Author	Cerebrum, Cerebellum, Medulla, Pons	Spinal Cord	Muscles	Peripheral Nerves
19. Rothmann	At nucleus of glossopharyngeal marked development of blood vessels; cells were degenerated and there was a diminished number of motor cells in the nuclei; same was true of vagus nucleus. In the height of the pyramidal tract there was still more marked absence of the motor ganglion cells; also in nucleus of hypoglossus; cerebellum small	Development of fine fibers was much diminished; many capillaries were present; almost complete absence of anterior (ganglion) horn cells and of Clark's columns; posterior horns normal; anterior roots small; many fibers lacked sheaths; posterior roots normal except in lumbar region (small); glia increased	Interstitial connective tissue increased; nuclei increased; increased fat between muscle fibers; muscle fibers, some gone; others replaced by small round cells; normal fibers also present; muscles pale	Nerves themselves were small; axis cylinders were small; connective tissue increased and the nuclei were numerous; incomplete myelinization; entrance of nerves into muscle fibers could be seen, but endplates were absent
20 and 21. Skoog (biopsy) 2 cases	Not one muscle bundle appeared normal; were very small; no hypertrophic fibers present; transverse striation gone; connective tissue and fat increased, especially between muscle bundles; nuclei increased
22. Skoog (biopsy)	Muscle pale and contained much fat; muscle bundles could be seen terminating abruptly in a replacing adipose tissue; much fat between bundles; no hypertrophic fibers; nuclei increased; blood vessels greatly thickened
23. Spiller 22 months	Normal (paracentral lobules small; Betz' cells few in number)	Normal	Increase in nuclei of connective tissue; muscle fibers were small; unusually large muscle fibers were not observed; transverse striations were well preserved; longitudinal were not so distinct; muscles have a hyaloid appearance; large amount of fatty connective tissue and increase in the nuclei of the connective tissue	Normal. Nerve fibers within the muscles from the sole of the foot appeared to be normal
24. Strauch (partial necropsy)	Muscles showed marked condition of atrophy; individual bundles were small and separated from each other by a large amount of fat; striations gone; fibers were narrow and varied in size; no hypertrophic fibers were present; nuclei increased, with karyokinetic figures	Marked but not very profound degenerative changes; myelin sheaths were well preserved; here and there it was thinned out; occasional breaks in the myelin sheath were present; the interstitial connective tissue was very much increased
25. Berghinz	Nerve cells of cerebellum small; hypoplasia and microgyria of cerebrum	Cells of anterior horns small and few
26-30. Mensi (5 cases)	Anterior horn cells reduced in number and are multipolar; large ganglion cells absent	Muscle fibers and bundles slender; cross striations absent or indistinct	No nerve endings could be found
1. Concetti 53 days	Cerebellum and Purkinje's cells were few and altered in shape; all layers of cerebrum reduced in volume; glia normal	Anterior roots smaller than normal; anterior horn cells few and small; large ganglion cells absent; Clark's columns normal; no changes in the glia; blood vessels and the meninges	Muscle fibers very small and some larger; some hypertrophic; striations normal; nuclei increased; no increase in interstitial connective tissue; no increase of nuclei; no sclerosis	A few fibers lacked myelin, but no degeneration was present
2. Openshaw 7½ years	Transverse striations absent fatty infiltration and signs of regeneration

We may perceive an illustration of the failure of the life of the hair follicles of the scalp, which must be the essential cause of early baldness; premature grayness is another example of early death. In the various forms of idiopathic muscular atrophy, we have true examples of abiosis; in these the muscular fibers, after full development, cease to maintain their own nutrition; they slowly waste and a large number of them ultimately perish. It is a defect of vital endurance, truly congenital, in so far as the tendency is concerned. We have further proof of its dependence on a congenital tendency in its occurrence in several members of the same family, chiefly in the males, the girls who do not suffer conveying the morbid tendency to their sons.

The neurons depend for vitality on the cell from which the fibers proceed; the groups of neurons which are differentiated in function differ also in their tendency to decay and in their degree of vitality. These neurons differ not only in the lapse of life, but also in the early stage; some are structurally complete sooner than others and thus are distinguished in the beginning of life as well as in its ending.

Whenever the nerve elements waste there is an overgrowth of the interstitial neuroglia, the connecting and supporting tissue which lies between them. The neuroglia is a residue of the embryonal tissue from which the nerve elements also develop. When there is local arrest of development of the latter, the embryonal tissue persists in tracts adjacent; the two elements, the neural and the neurologic, seem to have a common but inverse vitality; it is in consequence of this that the interstitial tissue overgrows when the nerve elements decay, and may be at first more conspicuous.

Assuming that the paresis of the musculature in this disease is due to an early abiotrophy, how can we explain the changes in the nervous system? It appears to us that a knowledge of the development of the nervous system may throw some light on this subject.

The nervous organs of the higher animals, including man, consist of enormously intricate systems of interwoven nerve cells or neurons. These neurons possess a nucleated cell body from which extremely attenuated processes, the nerve fibers, reach out to the most distant parts of the animal. These processes are the most characteristic parts of the neuron. The neurons are highly specialized in structure and exhibit profound physiologic differentiation; functional specialization among these elements has come to be so extreme that the nervous system may be described as one in which differentiation has reached to its very cells.

The neurons may be classified: (1) the afferent (sensory neuron) extending in general from the surface of the animal to the central organs and transmitting sensory impulses. (2) The efferent neurons connecting the central organs with the muscles, etc., and transmitting

efferent impulses, and finally (3) the association neurons which lie entirely within the central organ and connect one part of this organ with another (the association neurons far outnumber those of the other two classes and constitute the chief mass of these organs).

Almost all nervous operations in higher animals involve all three classes of neurons. The typical nervous reactions of these animals consist of a sensory stimulation followed by a motor response; this operation has been called a reflex. The ordinary reflex may be said to involve, in sequence, the activity of a receptor (sense organ), adjustor (central organs) and an effector (not neurons, but muscle fibers or gland cells). Our own reflexes are sometimes associated with consciousness and sometimes not.

From a study of the neuromuscular mechanism (which has no adjustors) of the sea anemone, we are bound to conclude that the central nervous organs (adjustors) were evolved only after the appearance of sense organs and muscle.

In studying the reactions of one of our common sponges (*Stylotella*), Parker was impressed with the extreme slowness with which the animal responded to a stimulus; transmission in the stylotella, resembles very closely the kind of transmission seen in ciliated epithelium. This probably represents a primitive form of protoplasmic transmission, a forerunner of the true nervous impulse. Sponges probably possess no true nervous tissue; their muscles are brought into action almost entirely by the direct effect of the stimulus, rather than through nerves, and this accounts for the slow response to external disturbances. The state of the sponges suggests that nerve and muscle have not been differentiated simultaneously, but that muscle preceded nerve in its evolution and that sponges represent animals with effectors, but without differentiated receptors. If it may be asserted that the sense organ preceded the central nervous organ, it may also be maintained that muscles preceded sense organs. Thus the three elements of the reflex arc of higher animals were probably evolved separately and in the order of effector, receptor and adjustor. This is proved by certain muscles of man. The sphincter of the iris, in lower vertebrates (though under influence of nerves) was shown by Stemace to be directly stimulated by light; also the embryonic vertebrate heart, which beats before it has become invaded by nerves.

It seems, therefore, that muscle arose first, and the simple effectors thus produced were the first elements of the neuromuscular mechanism. These effectors were directly stimulated and consequently slow in action. They afforded tissue around which nervous tissue first differentiated in the form of sense organs or receptors, whose function it was to serve as triggers to initiate muscle action quickly. As these receptors became more highly developed, a third element, the central

nervous organ, arose from the nervous element between the receptor and the effector. This organ, the adjustor, served as a means of conducting and modifying the sensory impulses on their way from the receptor to the effector, and ultimately it served as a storehouse for the nervous experience of the individual, as the seat of his intellectual life.

There is sufficient evidence at hand to show that Nissl degeneration, followed by gradual atrophy and disappearance, occurs when neurons are deprived of their function by any cause, as the removal of a limb.

It is reasonable to suppose (in view of the dependence of proper neural development on proper muscular development) that the more extensive and intensive is the pathologic condition of the musculature and the earlier it develops, the more extensive and intensive will the pathologic process be in the nervous system; data derived from necropsies on cases of amyotonia congenita substantiate this assumption.

In accordance with this hypothesis, many clinical findings, which could not previously be correlated with the necropsy findings, seem to find a rational explanation.

From what has been said, we would expect but little involvement of the nervous system in cases in which the onset of the disease was delayed for a number of months after birth, and in cases in which the muscle was but slightly affected; on the contrary, the earlier in fetal life and after birth the muscles become affected, and the more severe the process, the more severe will the pathologic process be in the nervous system.

To summarize: We believe that amyotonia congenita is primarily a muscular disease, a disease which is due to an inborn, inherent defect in the vitality of the musculature; and as proper neural development depends on proper muscle development, the earlier, the more intensively and the more extensively the musculature becomes involved in this abiotrophy, the earlier, the more intensively and extensively will the nervous system become involved.

CLASSIFICATION OF MYOTONIA CONGENITA

There is no group of diseases which offers such difficulties in its classification as do the progressive muscular atrophies; various classifications have been suggested, but not one is sufficiently comprehensive to include all known forms, nor sufficiently differentiated to exclude varieties which pathologically do not belong to the group.

Clinicians for many centuries have described progressive muscular wasting. Pictures and images in stone and wood of the muscular atrophies and muscular dystrophies dating from the fifteenth, sixteenth

and seventeenth centuries are in existence. Van Sweeten, Abercrombie and others gave general descriptions. This group was first broken into by Duchenne, in 1849, by the loose description of a special type, which a year later Aran supplemented. Cruveilhier, in 1853, and Luys, in 1860, sharpened the picture somewhat by their demonstration of the exclusive implication of the anterior horns. In 1853, Duchenne set aside the pseudohypertrophies, the muscular features and varieties of which were later demonstrated by Eulenberg (1866), Charcot, Leyden and Dejerine. Thus it took thirty years for the sorting out of this medley of muscular atrophies.

The very large and extremely motley group of muscular dystrophies has also been built up of a variety of forms since Duchenne, in 1849, first described the fatty pseudohypertrophies, and later, in 1868, spoke of them as myoscleroses. Leyden (1876) and Möbius (1879) described certain hereditary forms, while Erb, in 1883, first brought some order into the confusion of the atrophies and dystrophies by showing that in certain forms the lesion was predominantly muscular and not nervous. The myopathies make a fairly consistent group, although the forms may not resemble one another clinically at different periods of their development, yet they have a number of common factors.

In 1891, Werdnig described a new form of spinal progressive muscular atrophy in two sisters. Hoffman substantiated the findings of Werdnig and reported twenty cases in three families, all afflicted with the same disease. This disease has since become known as the Werdnig-Hoffman type of spinal progressive muscle atrophy of children; and finally, in 1900, Oppenheim described a syndrome which he thought could be differentiated from all previously described varieties; future observations proved the correctness of his investigations and the disease is now known as Oppenheim's disease, or "amyotonia congenita."

The spinal motor neuron is differentiated into three structures: the anterior horn cell, the motor nerve fiber and the muscle plate; if a clinical division could be made in strict accordance with the pathologic alterations of these structures, great advance toward the simplification of the classification of this group of diseases would be made.

The classification of Kügelgen seems to be the best:

- A. Muscular dystrophies (myopathies)
 - I. Pseudohypertrophic (Duchenne)
 - II. Juvenile type (Erb)
 - III. Facioscapulohumeral (Landouzy, Dejerine)
 - IV. Distal type (Gowers)
 - V. Myotonia atrophica
 - VI. Mixed and transitional types
- B. Amyotonia congenita

TABLE 4.—DIFFERENTIAL DIAGNOSIS

	Muscular Dystrophy	Werding-Hoffman Type	Oppenheim's Disease
Heredity	Usually hereditary and familial	Hereditary and familial	Not hereditary; rarely familial
Onset	Gradual during childhood; rarely in infancy (2 to 7 years), after learning to walk.	Gradual, usually in the second half of first year; born healthy; usually before walking was accomplished	Congenital or in the first few months of life; suddenly, following acute illness
Muscles affected	Pectoralis major, rhomboides, serratus anterior most often the seat of early atrophy; bulbar muscles hardly ever affected.	Muscles of pelvic girdle and muscles of small of back first to be affected; later muscles of back, shoulders, thighs, arms; bulbar muscles rarely affected	Muscles of legs most frequently involved; less marked involvement of arms, back, neck; bulbar muscles not infrequently affected (face)
Atrophy	Present and visible in some muscles; pseudo-hypertrophy visible in other muscles	Atrophy present and visible; no hypertrophic muscles observed	Atrophy not present; if present not visible; no hypertrophic muscles observed
Tendon flexes	Disappeared gradually; the Achilles is apt to persist or be increased, with hypertrophy not observed	Absent; never returned after disappearance	Absent or feeble; returned with improvement in muscle power
Fibrillary twitchings	Twitching and tremors sometimes seen	Not observed
Electrical actions	Quantitative diminution to total absence	Reaction of degeneration	Quantitative diminution to total absence
Course	Gradual deterioration	More rapid deterioration; usually died in childhood	Gradual improvement; never complete recovery
Pathology: Brain	Normal; head in a few cases asymmetrical; parietal and temporal bones prominent; prognathism; mental deficiency, idiocy, epilepsy not infrequently observed	Mentality usually normal; no pathologic lesions found in the brain	Mentality usually normal; backwardness in a small percentage; usually normal; rarely showed atrophy; absence of cells in motor nuclei
Spinal cord	Normal	Absence of anterior horn ganglion cells in the whole cord up to medulla; the cells showed swelling, atrophy, diminution of chromophilic substance and eccentric position of nuclei; myelin sheaths showed degenerative changes; slight changes in tract of Goll and pyramidal tracts; marked degeneration of anterior horns	The motor cells of anterior horns were reduced in number; anterior horns and roots were small; degenerative signs were few; inflammatory signs were lacking
Peripheral nerves	Normal	Marked signs of degeneration	Reduced in size; showed deficient myelination; end-plates visible in only few cases
Muscles	Simple atrophy and hypertrophy of muscle fibers; pseudohypertrophy of muscles due to infiltration with fat; fat increased; connective tissue increased; muscle fibers showed splitting, division and vacuolation; nuclei increased; hypertrophic fibers lost their polygonal shape; transverse striation was obscure	Simple atrophy; more or less fat deposition between the muscle bundles; muscles "en miniature"; no increase of nuclei; fatty or amyloid degeneration of muscle fibers; rarely hypertrophic fibers seen	Most muscle fibers were small; many were hypertrophic; intermuscular fat and connective tissue increased; striations well preserved; nuclei apparently increased
Contractures	Pes equinus; deformities of elbows, knees, hands and feet; short hands and short feet	Mostly of fingers and toes in form of claw deformities and equinovarus; deformities of back	Contractures of arms more frequent than in other forms; pes equinus; deformities of back (postural)

and seventeenth centuries are in existence. Van Sweeten, Abercrombie and others gave general descriptions. This group was first broken into by Duchenne, in 1849, by the loose description of a special type, which a year later Aran supplemented. Cruveilhier, in 1853, and Luys, in 1860, sharpened the picture somewhat by their demonstration of the exclusive implication of the anterior horns. In 1853, Duchenne set aside the pseudohypertrophies, the muscular features and varieties of which were later demonstrated by Eulenberg (1866), Charcot, Leyden and Dejerine. Thus it took thirty years for the sorting out of this medley of muscular atrophies.

The very large and extremely motley group of muscular dystrophies has also been built up of a variety of forms since Duchenne, in 1849, first described the fatty pseudohypertrophies, and later, in 1868, spoke of them as myoscleroses. Leyden (1876) and Möbius (1879) described certain hereditary forms, while Erb, in 1883, first brought some order into the confusion of the atrophies and dystrophies by showing that in certain forms the lesion was predominantly muscular and not nervous. The myopathies make a fairly consistent group, although the forms may not resemble one another clinically at different periods of their development, yet they have a number of common factors.

In 1891, Werdnig described a new form of spinal progressive muscular atrophy in two sisters. Hoffman substantiated the findings of Werdnig and reported twenty cases in three families, all afflicted with the same disease. This disease has since become known as the Werdnig-Hoffman type of spinal progressive muscle atrophy of children; and finally, in 1900, Oppenheim described a syndrome which he thought could be differentiated from all previously described varieties; future observations proved the correctness of his investigations and the disease is now known as Oppenheim's disease, or "amyotonia congenita."

The spinal motor neuron is differentiated into three structures: the anterior horn cell, the motor nerve fiber and the muscle plate; if a clinical division could be made in strict accordance with the pathologic alterations of these structures, great advance toward the simplification of the classification of this group of diseases would be made.

The classification of Kügelgen seems to be the best:

- A. Muscular dystrophies (myopathies)
 - I. Pseudohypertrophic (Duchenne)
 - II. Juvenile type (Erb)
 - III. Facioscapulohumeral (Landouzy, Dejerine)
 - IV. Distal type (Gowers)
 - V. Myotonia atrophica
 - VI. Mixed and transitional types
- B. Amyotonia congenita

TABLE 4.—DIFFERENTIAL DIAGNOSIS

	Muscular Dystrophy	Werding-Hoffman Type	Oppenheim's Disease
Heredity	Usually hereditary and familial	Hereditary and familial	Not hereditary; rarely familial
Onset	Gradual during childhood; rarely in infancy (2 to 7 years), after learning to walk.	Gradual, usually in the second half of first year; born healthy; usually before walking was accomplished	Congenital or in the first few months of life; suddenly, following acute ailment
Muscles affected	Pectoralis major, rhomboidei, serratus anterior most often the seat of early atrophy; bulbar muscles hardly ever affected.	Muscles of pelvic girdle and muscles of small of back first to be affected; later muscles of back, shoulders, thighs, arms; bulbar muscles rarely affected	Muscles of legs most frequently involved; less marked involvement of arms, back, neck; bulbar muscles not infrequently affected (face)
Atrophy	Present and visible in some muscles; pseudo-hypertrophy visible in other muscles	Atrophy present and visible; no hypertrophic muscles observed	Atrophy not present; if present not visible; no hypertrophic muscles observed
Tendon flexes	Disappeared gradually; the Achilles is apt to persist or be increased, with hypertrophy not observed	Absent; never returned after disappearance	Absent or feeble; returned with improvement in muscle power
Fibrillary twitches	Twitching and tremors some times seen	Not observed
Electrical actions	Quantitative diminution to total absence	Reaction of degeneration	Quantitative diminution to total absence
Course	Gradual deterioration	More rapid deterioration; usually died in childhood	Gradual improvement; never complete recovery
Pathology: Brain	Normal; head in a few cases asymmetrical; parietal and temporal bones prominent; prognathism; mental deficiency, idiocy, epilepsy not infrequently observed	Mentality usually normal; no pathologic lesions found in the brain	Mentality usually normal; backwardness in a small percentage; usually normal; rarely showed atrophy; absence of cells in motor nuclei
Spinal cord	Normal	Absence of anterior horn ganglion cells in the whole cord up to medulla; the cells showed swelling, atrophy, diminution of chromophilic substance and eccentric position of nuclei; myelin sheath showed degenerative changes; slight changes in tract of Goll and pyramidal tracts; marked degeneration of anterior horns	The motor cells of anterior horns were reduced in number; anterior horns and roots were small; degenerative signs were few; inflammatory signs were lacking
Peripheral nerves	Normal	Marked signs of degeneration	Reduced in size; showed deficient myelization; endplates visible in only few cases
Muscles	Simple atrophy and hypertrophy of muscle fibers; pseudohypertrophy of muscles due to infiltration with fat; fat increased; connective tissue increased; muscle fibers showed splitting, division and vacuolation; nuclei increased; hypertrophic fibers lost their polygonal shape; transverse striation was obscure	Simple atrophy; more or less fat deposition between the muscle bundles; muscles "enminiature"; no increase of nuclei; fatty or amyloid degeneration of muscle fibers; rarely hypertrophic fibers seen	Most muscle fibers were small; many were hypertrophic; intermuscular fat and connective tissue increased; striations well preserved; nuclei apparently increased
Contractures	Pes equinus; deformities of elbows, knees, hands and feet; short hands and short feet	Mostly of fingers and toes in form of claw deformities and equinovarus; deformities of back	Contractures of arms more frequent than in other forms; pes equinus; deformities of back (postural)

C. Progressive nuclear atrophies (myelopathies)

- I. $\left\{ \begin{array}{l} a. \text{ Chronic anterior poliomyelitis} \\ b. \text{ Aran-Duchenne's disease} \\ c. \text{ Werdnig-Hoffman type} \end{array} \right.$
- II. Bulbo-pontive types (Möbius-Heubner)
- III. Pontomesencephalic forms

D. Spinal neuritic atrophies

- I. Charcot-Marie-Tooth type
- II. Tabetic type (Dejerine-Sottas)
- III. Peroneal-arm type (Sainton-Haevel)

The two diseases from which amyotonia congenita is to be differentiated are from the spinal progressive muscular atrophy (type Werdnig-Hoffman) and from the pseudohypertrophic form of muscular dystrophies (type Duchenne). In some respects it simulates both; in many it differs considerably. The differential points are noted in Table 4.

Although the main points have been stated in the differential diagnosis, these three diseases are not so sharply defined as it would appear. Thus at times, in true cases of muscular dystrophy, there is found a true reaction of degeneration; a few observers have also noted fibrillary twitchings in muscular dystrophies. The presence of mental deficiency, idiocy, and epilepsy can hardly be explained in the strength of pure coincidence; they occur too often; at times, in true cases, the anterior horn cells were also involved (Clarke, Heubner, Peck, Erb, Schultze, Singer).

Improvement is the characteristic symptom of amyotonia congenita, yet in many cases there was progressive deterioration without ever showing any amelioration; on the contrary, progressive deterioration is characteristic of myopathies, and yet a few isolated cases have shown complete arrest of symptoms (Mariana). Return of knee jerks which is most usually found in amyotonia congenita, has also been observed in the dystrophies (Jendrassik).

From a study of all the cases reported and from the facts mentioned we are inclined to group amyotonia with the myopathies and not with the myelopathies; amyotonia congenita seems to be a connecting link between muscular dystrophies, on one hand, and spinal progressive muscular atrophies, on the other.

I am indebted to Dr. Carlucci for the translation of the Italian articles. I am also greatly indebted to Mr. F. Place of the New York Academy of Medicine for his invaluable assistance in searching and compiling the literature on this subject.

316 West Ninety-Fourth Street.

REFERENCES IN CASE REPORTS

1. Archangelsky and Abrikosoff: Arch. f. Kinderh., 1911, **56**, 101.
2. Ashby: Brit. Med. Jour., 1909, **2**, 1153.
3. Ausset: Echo méd. du nord., 1908, **12**, 143.
4. Baudouin: Semaine méd., 1907, **37**, 240.

5. Batten: *Brain*, 1903, **26**, 147.
6. Beling: *Jour. Nerv. and Ment. Dis.*, 1914, **41**, 220.
7. Beevor: *Proc. Roy. Soc. Med.*, 1907-1908, Part I, *Neurol. Sect.*, p. 1.
8. Berghinz: *Riv. di clin. pediat.*, 1911, **9**, 480.
9. Bernhard: *Deutsch. Ztschr. f. Nervenh.*, 1904, **26**, 78.
10. Berti: *Pediatrics*, 1905, **13**, 134.
11. Bienfait: *Ann. Soc. méd.-chir. de Liège*, 1913, **52**, 234.
12. Bing: *Med. Klin.*, 1907, **3**, 10.
13. Brunard: *Clinique Brux.*, 1908, **22**, 401.
14. Carcupino: *Riv. di clin. pediat.*, 1911, **9**, 762.
15. Cattoneo: *Clin. mod.*, 1906, **11**, 282.
16. Chéné: *Thèse de Paris*, 1910.
17. Collier and Wilson: *Brain*, 1908, **31**, 1.
18. Collier and Holmes: *Brain*, 1909, **32**, 269.
19. Collier: *Proc. Roy. Soc. Med.*, 1915, **8**, *Neurol. Sect.*, 71.
20. Comby: *Arch. de méd. d. enf.*, 1906, **9**, 552; *Bull. Soc. de pediat. de Paris*, 1907, **9**, 249.
21. Concetti: *Riv. di clin. pediat.*, 1911, **9**, 1; *ibid.*, 1913, **11**, 1.
22. Coombs: *Brit. Med. Jour.*, 1907, **1**, 1414.
23. Cotteril: *Edinb. Med. Jour.*, 1913, **10**, 519.
24. Councilman and Dunn: *Am. Jour. Dis. Child.*, 1911, **2**, 340.
25. Courtney and Eaton: *Boston Med. and Surg. Jour.*, 1914, **170**, 117.
26. Dunn: *Boston Med. and Surg. Jour.*, 1914, **171**, 191.
27. Duthoit: *Arch. de méd. d. enf.*, 1912, **15**, 881.
28. Feer: *Cor.-Bl. f. schweiz. Aerzte*, 1912, **42**, 719.
29. Fletcher (for Smith): *Proc. Roy. Soc. Med.*, 1913-1914, *Sect. Dis. Child.*, p. 117.
30. Foot: *Am. Jour. Dis. Child.*, 1913, **5**, 359.
31. Faber: *Am. Jour. Dis. Child.*, 1917, **13**, 305.
32. Frevez: *Scalpel et Liège méd.*, 1913, **65**, 568.
33. Fearnside: *Proc. Roy. Soc. Med.*, 1914-1915, **8**, *Neurol. Sect.*, p. 49.
34. Gastonguay: *Bull. méd. de Quebec*, 1908-1909, **10**, 97.
35. Gatti: *Liguria med.*, 1913, **7**, 165.
36. Gordon: *Jour. Nerv. and Ment. Dis.*, 1913, **40**, 109.
37. Griffith: *Tr. Am. Pediat. Soc.*, 1910, **22**, 184; *Am. Jour. Med. Sc.*, 1911, **142**, 165.
38. Guinon and Gauducheau: *Bull. Soc. de pédiat. de Paris*, 1911, **13**, 341.
39. Guillemot: *Bull. Soc. de pédiat. de Paris*, 1907, **9**, 171.
40. Gött: *Ztschr. f. Kinderh.*, 1912, **8**, 216.
41. Haberman: *Am. Jour. Med. Sc.*, 1910, **139**, 383.
42. Hertz and Johnson: *Proc. Roy. Soc. Med.*, 1913-1914, **7**, *Clin. Sect.*, 30.
43. Hummel: *Jour. Nerv. and Ment. Dis.*, 1910, **37**, 749.
44. Hartenberg: *Arch. de Neurol.*, 1909, **1** and **2**, 161.
45. Jovane: *La Pediatrics*, 1906, **14**, 190.
46. Kaumheimer: *Jahrb. f. Kinderh.*, 1913, **78**, *Suppl.*, p. 170.
47. Keersmaker: *Clinique, Brux.*, 1913, **27**, 273.
48. Kundt: *Inaug. Diss.*, Leipzig, 1905.
49. Koch: *Demonstration an der 20 Versammlung der Südwestdeutschen vom Niederrhein., Westfälische Vereinigung für Kinderheilkunde zu Wiesbaden*, April 13, 1913. *Monatschr. f. Kinderh.*, 1913-1914, **12**, 353.
50. Laffer: *Ohio State Med. Jour.*, 1909, **5**, 609.
51. Leclerc: *Gaz. d. hôp.*, 1907, **80**, 1683.
52. Lereboullet and Baudouin: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1909, **26**, 1162.
53. Lungenbühl: *Deutsch. med. Wchnschr.*, 1907, **33**, 1439.
54. Marburg: *Arb. a. d. neurol. Inst. a. d. Wien. Univ.*, 1911, **19**, 133.
55. Mensi: *Riv. di clin. pediat.*, 1912, **10**, 527.
56. Moussous and Carles: *Jour. de méd. de Bordeaux*, 1909, **39**, 697.

57. Muggia: *Pediatrics*, 1903, **11**, 179.
58. Mettenheimer, Götzky and Weihe: abstr., *Neurol. Centralbl.*, 1915,, **34**, 655.
59. Naish: *Proc. Roy. Soc. Med.*, 1910, **3**, Part 2, *Neurol. Sect.*, 95.
60. Oliari: *Pédiatrie*, 1911, **9**, 515.
61. Openshaw: *Proc. Roy. Soc. Med.*, 1910, **3**, Part I, *Clin. Sect.*, 39.
62. Orbison: *Jour. Nerv. and Ment. Dis.*, 1909, **36**, 204.
63. Oppenheim: *Monatschr. f. Psychiat. u. Neurol.*, 1900, **8**, 232; *Berl. klin. Wchnschr.*, 1904, **41**, 255; *Berl. klin. Wchnschr.*, 1912, **49**, 2435.
64. Pollock: *Arch. f. Kinderh.*, 1910, **53**, 373.
65. Pelz: Case presented before Verein für wissenschaftliche Heilkunde im Königsburg i. Pr., May 29, 1911.
66. Princeteau: Case reported in discussion of case of Moussous.
67. Purser: *Dublin Jour. Med. Sc.*, 1914, **137**, 241.
68. Reiner: *Berl. klin. Wchnschr.*, 1913, **1**, 1306.
69. Reyher and Helmholtz: *Jahrb. f. Kinderh.*, 1908, **67**, 1614.
70. Rosenberg: *Deutsch. Ztschr. f. Nervenhe.*, 1906, **31**, 130.
71. Rothmann: *Monatschr. f. Psychiat. u. Neurol.*, 1909, **25**, Suppl., p. 161.
72. Rocher in discussing case of Moussous said he had seen a case; no details.
73. Rad: *Festschrift des Cnopfschen Kinderspitals, Nuremburg*, 1914; no details. *Abstr.*, *Neurol Centralbl.*, 1915, **34**, 656.
74. Rietschel: *Deutsch. med. Wchnschr.*, 1911, **37**, 1371.
75. Schippers: *Nederl. Tijdschr. v. Geneesk.*, 1911, **1**, 1471.
76. Schüller: *Wien. klin. Wchnschr.*, 1904, **17**, 722; *Neurol. Centralbl.*, 1905, **24**, 1783.
77. Schlivek: *Arch. Pediat.*, 1910, **27**, 34.
78. Skoog: *Jour. Am. Med. Assn.*, 1910, **55**, 364; *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1914, *Orig.*, **27**, 357.
79. Snow: *Jour. Am. Med. Assn.*, 1912, **58**, 745.
80. Sorgente: *Pediatrics*, 1906, **14**, 358.
81. Simonini: *Riv. di. clin. pediat.*, 1907, **5**, 845.
82. Silvestri: *Gazz. d. osp.*, 1909, **30**, 577.
83. Spiller: *Univ. Pennsylvania Med. Bull.*, 1905, **17**, 342.
84. Strauch: *Am. Jour. Dis. Child.*, 1914, **8**, 298; *ibid.*, 1915, **10**, 16.
85. Sutherland: *Proc. Roy. Soc. Med.*, 1914-1915, **8**, *Sect. Dis. Child.*, 28.
86. Thompson: *Brain*, 1908, **31**, 160.
87. Thorspecken: *Jahrb. f. Kinderh.*, 1912, **76**, 300.
88. Tobler: *Jahrb. f. Kinderh.*, 1906, **66**, 33.
89. Variot and Chatelin: *Rev. neurol.*, 1911, **21**, 138.
90. Variot and Devillers: *Bull. Soc. de pédiat. de Paris*, 1907, **9**, 246.
91. De Villa: *Arch. de méd. d. enf.*, 1916, **19**, 137.
92. Wynter: *Proc. Roy. Soc. Med.*, 1907-1908, Part I, *Clin. Sect.*, 48.
93. Zahorsky: *Am. Jour. Obst.*, 1910, **62**, 1132.
94. Zappert: *Jahrb. f. Kinderh.*, 1901, **53**, 125.
95. Wimmer: *Arch. Psychol.*, 1912, **42**, 960.

GENERAL REFERENCES

96. Cassirer: *Handbuch der Neurologie*, Lewandowsky, 1911, **2**, 230.
97. Douškov: *Neurol. Vestnik*, 1909, **16**, 118.
98. Ivanoff: *Kharkov. Med. Jour.*, 1911, **12**, 311.
99. Monton: *Med. contemp.*, Lisbon, 1911, **29**, 395.
100. Araos-Alfaro: *Semana méd.*, Buenos Aires, 1913, **20**, 745.
101. Aronde: *Deutsch. med. Wchnschr.*, 1916, **42**, 467.
102. Garusso: *Rev. asoc. méd. argen.*, Buenos Aires, 1915, **23**, 949.
103. Klose: *Jahrb. f. Kinderh.*, 1916, **82**, 347.
104. Gittings and Pemberton: *Am. Jour. Med. Sc.*, 1912, **144**, 732.
105. Gayane: *Rev. clin. de Madrid*, 1909, **1**, 457 (article could not be obtained for review).

DIAGNOSTIC SIGNS FROM THE SCALENI, INTER-COSTAL MUSCLES AND THE DIAPHRAGM IN LUNG VENTILATION *

C. F. HOOVER, M.D.
CLEVELAND

During the past few years, respiration has come in for a bountiful share of physiologic and clinical research, but all of the research has been directed toward gaining some understanding of the exquisitely nicely balanced relations of excitatory and inhibitory influences which modify the rate, rhythm and amplitude of respiration.

Chemistry of the blood in its relation to respiratory function has also been the subject of much research, but the simpler problem of lung ventilation and its clinical analysis has been neglected. In every clinical examination we should form some definite idea about the volume, density and extensibility of the upper and lower lobes of the lungs. An understanding of these three physical attributes is the goal toward which most methods of physical examination of the lungs have been directed. Density of the lung, with some adventitious signs, has occupied the attention of clinicians much more than volume and extensibility of the lung.

To form a clear estimate of volume and extensibility of the lung we must have a clear conception of the physiologic mechanism by which lung ventilation is accomplished. In every case we must estimate:

1. The inspiratory enlargement of the thoracic cage in three dimensions.
2. The relative height of that portion of the diaphragm underlying the heart, and the height of the two leaves of the diaphragm underlying the lung.
3. The share of the scalmi in the movement of the upper four ribs.
4. The share of the intercostal muscles in the movements of all the ribs from the second rib to the twelfth.
5. Beside the above named diagnostic points, we must also differentiate the evidences of diaphragmatic activation from the evidences of diaphragmatic excursion.

In other words, to have a clear conception of the ventilatory function of the lung we must in every case point out the evidences of the functions of the scalmi, the intercostal muscles and the diaphragm.

* Submitted for publication May 29, 1917.

* From the Medical Department of Lakeside Hospital.

Briefly stated, the function of the scaleni muscles is solely to form a point of fixation in the first rib from which the second, third and fourth ribs are elevated. The increase of the anteroposterior and transverse diameters of the thorax is accomplished entirely by the intercostal muscles. The increase of the longitudinal diameter of the thorax is due solely to the descent of the diaphragm. These are the simpler facts, but the diagnostic problems which arise in clinical work require us to recognize what modifications of the respiratory excursion of the thorax betray a paralysis of the scaleni muscles, or paralysis of the intercostal muscles, or paralysis of the diaphragm.

We must also differentiate between evidences of activation of the diaphragm and evidences of excursion of the diaphragm.

I shall also show how we can recognize moderate depression of the middle portion of the central tendon of the diaphragm, as occurs in enlargement of the right ventricle of the heart and with small amounts of fluid in the pericardial sac. We can also recognize a depression of the left lateral portion of the central tendon due to enlargement of the left ventricle when the right ventricle is not enlarged.

By studying the inspiratory excursions of the costal margins we can recognize various degrees of depression of the muscular leaves of the diaphragm, namely: (a) when the under surface of the leaf is convex, as in very large pleural effusions; (b) when the leaf approximates a plane, as in moderate effusions; and (c) when the convexity of the upper surface of the leaf is increased, as occurs in hepatic enlargement and accumulations of pus or fluid between the diaphragm and liver. This can be learned by studying the inspiratory excursion of the median and lateral portions of the costal margins. This is all possible because the movement of the costal margins expresses accurately the balance between the intercostal muscles and diaphragm in their contest for mastery of the costal margins.

The median portions of the diaphragm are much less arched than the lateral portions, consequently much less depression of the median portion of the diaphragm is necessary to modify the normal excursion of the internal portion of the costal borders than is required to modify the normal excursion of the external portion of the costal borders.

With this general statement of the argument I shall proceed to illustrate the specific points by a number of clinical and experimental data.

Ventilation of the Upper Lobes of the Lungs.—Long ago the observation was made that the infraclavicular region exhibited an "undulatory movement during inspiration." This undulatory movement is due to the varying size of the upper five ribs. The lengths of the upper five ribs increase from the first to the fifth.

During inspiration the first rib is not elevated, but the second, third, fourth and fifth ribs are elevated by the so-called bucket handle move-

ment. The maximum movement of a rib will be in that portion farthest from the axis of rotation, consequently the external portion of the rib will move through a greater distance than the parts nearer the axis of rotation.

The distance through which a rib will move in response to an inspiratory activation of the intercostal muscles will be limited by the extensibility of the underlying lung. The movements of the upper five ribs faithfully mirror the movement of the underlying lung, consequently any disease which will impair the extensibility of the lung will modify the normal undulatory movement of the upper five ribs.

Any disease of the pleura, occlusion of a bronchus, or inflammatory process in a lung will diminish its extensibility. Extensibility is the first attribute which is modified in any inflammation of the lung. This diminution of extensibility can be detected before any increase of density is demonstrable. Consequently, the sign bears a very important significance in the early recognition of pulmonary tuberculosis of the upper lobes.

The undulatory movement varies in different normal persons just as the pitch of the percussion note varies. The more flexible the cartilage of the ribs the more active the bucket handle movement will be.

This phenomenon is observed best by the examiner when standing at the right of the recumbent patient. The examiner should use his left hand. Place the tip of the ring finger on the second rib at the midclavicular line, the tip of the middle finger on the third rib midway between the midclavicular and the anterior axillary line, and the tip of the index finger on the fourth rib in the anterior axillary line. The patient is then instructed to make a moderately rapid and moderately deep inspiratory movement. The finger on the third rib will be observed to move further than the finger on the second rib and the finger on the fourth rib will move further than the finger on the third rib. The movement in each rib from above downwards succeeds and exceeds that in the rib just above.

Should there be only a moderate impairment or diminution of ventilation in the upper lobe, the three ribs will move in unison and move the same distance, so the undulatory phenomenon will be lost although all the ribs involved may exhibit a considerable excursion during inspiration. By comparing the undulatory movement on the two sides we have a very delicate method of comparing the amount of ventilation in the upper portions of the upper lobes.

Anything which will slightly diminish the amount of ventilation on one side or the other will cause a disparity in the undulatory movement between the two sides. We find this true in any disease which will encroach on the air spaces, or invade the interstitial tissue of the lung or occlude a bronchus or displace a part of the lung as occurs in

mediastinal tumor. The undulatory movement will be diminished on the left side when the heart is enlarged in an upward direction or when the pericardial sac is distended and also when the pleura is thickened so its extensibility is diminished.

Localized emphysema of an upper lobe of the lung will reveal a diminished undulatory movement because the ribs are in a partial inspiratory phase at the beginning of an inspiration.

If the sign is taken for exactly what it amounts to, namely, a diminished ventilatory volume of the upper part of the upper lobe, it will be of great diagnostic service. Further diagnostic signs must aid in determining what has contributed to a localized diminution of ventilatory function of the lung.

The greatest practical use of this sign rests on the fact that in all diseases of the lung a diminution of extensibility is demonstrable earlier than changes in volume or density of the lung can be demonstrated. Certainly in the early or latent periods of pulmonary tuberculosis, diminished extensibility can be demonstrated when no evidences of alteration in density or volume of the lung can be elicited, and also when all adventitious signs are absent.

An exact study of the comparative extensibility of the upper lobes should constitute a part of routine clinical examinations. In our experience at Lakeside Hospital, this procedure has been the source of many diagnostic successes, and it has also aroused many interesting diagnostic problems which otherwise would have escaped our observation.

Rôle of the Scaleni Muscles.—The following case gave rise to a study of the differentiation between the rôle of the scaleni and intercostal muscles in respiratory excursion of the upper five ribs.

A child about 2 years old in the children's ward at Lakeside Hospital, was admitted with well advanced signs of a congenital muscular disease. There was absolute paralysis of all the muscles which contribute to movements of the head on the spine. The respiratory excursion of the thorax presented a very unusual picture. During inspiration the manubrium with the first three ribs were drawn strongly downward and inward; the fourth ribs remained stationary but the fifth ribs and those below moved upward to an unusual extent. The subcostal angle widened much more than in normal children. Both hypochondria moved outward much more than in normal cases. There was, however, no inspiratory retraction of the suprasternal notch or of the supraclavicular spaces.

The exaggerated spreading of the hypochondria and descent of the first three ribs and manubrium with each inspiration presented a very unusual and perplexing problem for analysis. The question which arose was whether the entire picture was due solely to paralysis of the scaleni muscles, or whether the upper intercostal muscles also shared in the progressive muscular disease.

EXPERIMENTS

Experiment 1.—Under ether anesthesia the three scaleni muscles of the right side of a dog were exposed and cut immediately above the first rib. The first, second and third ribs of the right side were drawn downward with each inspiration. The fourth rib remained stationary and the fifth rib, with all those below it, moved upward as in a normal animal. On the left side the first rib remained stationary but the second, third, fourth and fifth ribs exhibited the usual normal undulatory movement already described. When the scaleni of the left side were cut as those of the right side were cut in the beginning of the experiment, the same phenomena of respiratory excursion were produced on the left side. The respiratory excursion of the dog's thorax was identically like that of the child's thorax.

Experiment 2.—A young dog about 1½ years old was given morphin and ether anesthesia. The sternomastoid and scapula of the right side with all its muscular attachments were removed so there were only the scaleni, intercostal muscles and diaphragm left. The respiratory excursion of the entire thorax was unchanged. Then the scaleni were cut on the right side and the same changes in respiratory excursion were plainly seen on the right side as described in Experiment 1. The scaleni of the left side were then severed and the same descent of the upper three ribs with fixation of the fourth rib and upward movement of the fifth ribs with those below occurred as in the former experiment.

If the upper end of the sternum was grasped with forceps and held in position so the manubrium could not descend during an inspiratory movement, there was a return to the normal inspiratory evolution of the upper ribs. When the manubrium was released the picture of the child with paralysis of the scaleni was again reproduced.

Experiment 3.—Under morphin and ether anesthesia the spinal cord of a dog was severed at the sixth cervical segment. The scaleni and diaphragm were thus preserved, but all the intercostal muscles were paralyzed. There was no inspiratory descent of the upper ribs or manubrium, but with each inspiratory descent of the diaphragm the upper lateral portions of the thorax were retracted. There was no elevation of the first ribs during inspiration.

Experiment 4.—The following experiment shows how the structure of the bony thorax may greatly modify the phenomena thus far described. A well grown, young dog which still had its puppy teeth, was given morphin and ether anesthesia for the purpose of making other observations, but incidentally the scaleni muscles on both sides were exposed and severed. Instead of the phenomena observed in our former experiments, the first ribs were drawn downward with each inspiration, the second ribs were drawn in an upward direction, so that the second ribs actually overrode the first ribs to a slight degree. The manubrium was not drawn downward. The second, third and fourth ribs exhibited the normal undulatory movement seen under normal conditions.

COMMENT

These experiments suffice to show that the scaleni do not contribute to the inspiratory elevation of any of the ribs. The scaleni simply supply an anchorage for the first ribs only, and the evolution of the ribs during inspiration from the second downward is accomplished entirely by the intercostal muscles. I have had the opportunity of seeing only the one clinical case of paralysis of the scaleni, so from our experimental experience on dogs we may expect to find the inspira-

tory movements of the upper four ribs to differ in patients, just as occurred in our dogs.

There may be an inspiratory descent in a caudad direction of only the first ribs with a normal evolution of all the ribs from the second rib downward, or there may be an inspiratory descent of the upper three ribs and manubrium with fixation of the fourth rib and elevation of all the ribs below the fourth. This will depend on the mobility of the upper ribs and the manubrium. If the upper ribs and manubrium form a comparatively rigid structure, then only the first rib will be drawn downward with each inspiration if the scaleni are paralyzed; but if the manubrium and upper ribs are quite flexible, as in the child described, then paralysis of the scaleni will cause the inspiratory excursion of the thorax to present a striking picture of increased spreading of the hypochondria and retraction in a caudad direction of the manubrium and upper three ribs.

The Diaphragm and Intercostal Muscles.—The diaphragm and intercostal muscles are antagonists in two ways: The intercostals serve to increase the anteroposterior and transverse diameters of the thorax, and the diaphragm serves to increase the longitudinal diameter of the thorax. Activation of the intercostal muscles will tend to diminish the longitudinal diameter of the thorax unless resisted by the diaphragm, and activation with excursion of the diaphragm will cause a diminution in the other two dimensions of the thorax, with narrowing of the subcostal angle, unless resisted by the intercostal muscles. Much confusion has been introduced into this subject by failure to differentiate the evidences of diaphragmatic activation from the evidences of diaphragmatic excursion, and also the failure to recognize the significance of the arch of the diaphragm as a whole, and the significance of varying curves of different parts of the diaphragm has led to much confusion and misinterpretation of the respiratory movements of the costal margins.

The modern interpretation of the function of the intercostal muscles and the diaphragm has hitherto rested on the work of Duchenne¹ of Boulogne. A critical review of Duchenne's work is interesting in the light of more modern writers and the author's observations on patients and animals.

Duchenne proposed the following problems in his work:

Does the diaphragm in its contraction constrict the lower part of the thorax by drawing the lower ribs downward, or, on the contrary, does the diaphragm increase the transverse and anteroposterior diameters of the lower half of the thorax by lifting the diaphragmatic ribs upward and outward?

1. Duchenne: *Recherches Electro-Physiologiques et Therapeutiques sur la Diaphragme*, 1853.

Does there exist a difference between the physiologic action of the diaphragm in its relation with the abdominal viscera and the action of the diaphragm when it is deprived of its visceral relations?

Finally, what is the mechanism of the action of the diaphragm on the thoracic walls?

Then follows an interesting historical summary of the study of the diaphragm which shows what difficulty attended the interpretation of the function of the diaphragm in conjunction with the spread of the hypochondria and widening of the subcostal angle.

The anatomists of antiquity recognized only one muscle of inspiration and ascribed to the diaphragm the duty of carrying the ribs upward and outward. But Galen recognized other muscles of respiration and ascribed to the diaphragm only the function of lifting and spreading the lower ribs. Vesalius, however, questioned this. He interpreted the activation of the diaphragm as resulting in an elevation of the diaphragm. Columbus (his pupil) denied this and said the diaphragm was depressed by inspiration, but that the diaphragm was relaxed during inspiration. Activation of the diaphragm constricted the lower ribs but owing to relaxation during inspiration, the diaphragmatic ribs were permitted to spread.

Borelli, the physicist, cited by Duchenne, was the first to claim that the diaphragm contracted during inspiration and increased the longitudinal diameter of the thorax, and by virtue of its attachments to the ribs must necessarily by its action constrict the lower part of the thorax. Borelli asserted the diaphragm could not act independently of the intercostal muscles.

The idea of Galen was forgotten until 1833, when Magendie again took up the idea and said that the spreading of the lower thorax from diaphragmatic contraction and descent was due to the resistance of the viscera under the vault of the diaphragm, and as the ribs were readily moved, the compression of the viscera caused increase in the transverse diameter of the upper abdomen and thus pushed the ribs outward. Duchenne says Magendie never supported his idea, however, by any animal experiment.

In 1843 Beau and Maissiat undertook to establish the doctrine of Galen by experimental methods. They cut the lower six intercostal structures through from the sternum to the vertebrae on both sides after cutting the scaleni and all other thoracic muscles which might share in respiratory excursion. Only the upper intercostals and the diaphragm were left and the lungs were collapsed. Beau and Maissiat observed that under these conditions the diaphragmatic ribs were elevated and the base of the thorax was widened. When the diaphragm was hastily cut away the base of the thorax was immobilized. They confirmed Galen's observation, but said nothing about the rôle of the viscera underneath the diaphragm contributing to the spread of the lower thorax during inspiration. M. T. de Brou² repeated the experiments of Beau and Maissiat and came to just the opposite conclusion.

2. de Brou, M. T.: *Gazz. Med.*, 1843, p. 344.

As we shall see later, the differing results of these observers was due merely to a difference in the vaults of the diaphragms of the dogs used by the experimenters. De Brou evidently used a dog which had less convexity to his diaphragm than had the dog which was used by Beau and Maissiat. Under the experimental conditions, a dog with a long thorax and high arch to his diaphragm would show an inspiratory widening of the subcostal angle, whereas a dog with a shorter thorax with less convexity to his diaphragm would show an inspiratory narrowing of the subcostal angle. The reason for this will be discussed later.

Up to the time of Duchenne, great doubt existed as to whether or not the diaphragm played any rôle in inspiratory widening of the base of the thorax. Since Duchenne's experiments, however, widening of the subcostal angle has been ascribed in part to diaphragmatic action. It is this error which has caused so much confusion and misinterpretation of the respiratory movements of the costal borders.

Duchenne applied electrodes over the phrenic nerve in front of the scalenus anticus and observed protrusion of the epigastrium and an outward movement of the costal margin on the affected side. This is an observation which is unreliable, because one could not be sure that the intercostals of the affected side were not also activated.

Duchenne then exposed the phrenic nerve of a dog and stimulated the nerve with an electric current and observed the same movements of the epigastrium and costal margin. This is contrary to the results which I³ procured by stimulating the exposed phrenic nerves of dogs. We must, however, take into account that Duchenne's observations were made on dogs with unopened abdomens, whereas my observations were made on dogs with abdomens opened so I could see the movements of the diaphragm. In my experiments the costal margins were drawn violently toward the median line when the exposed phrenic nerves were stimulated by an electric current.

Duchenne repeated his experiments on both horses and dogs and got the same results, but in both horses and dogs, phrenic activation caused retraction of the hypochondria and narrowing of the subcostal angle when the abdomens were opened and all the viscera were removed from the upper abdomen. Duchenne says that such diaphragmatic activation has an expiratory result. We will see later that Duchenne's animals would have shown a narrowing of the subcostal angle from isolated phrenic activation had the abdominal wall been opened so as to allow the entrance and exit of air during respiration. It was not

3. Hoover, C. F.: The Functions of the Diaphragm and Their Diagnostic Significance, *THE ARCHIVES INT. MED.*, 1913, **12**, 214.

necessary to disturb the abdominal viscera to change the direction in which the costal margins moved during phrenic contraction.

In a former communication^s I described several experiments in which it was clearly proved that when the diaphragm was activated by electric stimulation the costal margins were violently drawn toward the median line. All these experiments, however, were made with the abdomen opened so the movements of the diaphragm were plainly visible from its lower surface.

In the meantime a patient suffering from fracture of the sixth cervical vertebra was observed, in whom there was complete motor paralysis of all muscles supplied below the sixth cervical segment. The scaleni and diaphragm were preserved, but all the intercostal muscles were paralyzed. During inspiration the first ribs were stationary and the hypochondria were retracted with each inspiration. The subcostal angle was much narrowed with each inspiration. The entire costal margins on both sides were drawn toward the median line with each contraction of the diaphragm.

Experiment 5.—A dog of the setter type was anesthetized with ether and then the cervical cord was sectioned at the sixth segment. To our surprise we found a respiratory movement of the thorax which was quite different from what we expected to find in view of our former experiments and clinical observations. The first ribs were stationary. There was only inspiratory retraction of the ribs and intercostal spaces in the upper thorax, but in the lower thorax there was a very different picture. From the ninth to the twelfth ribs inclusively there was an outward movement with distinct widening of the subcostal angle during inspiration. The character of the movement, however, was not such as we see when the intercostal muscles are active. The outward movement of the lower ribs was evidently a passive and not an active movement. The movement was quite like that observed by Beau and Maissait and by Duchenne in their animal experiments.

An incision was then made in the linea alba so the peritoneal cavity was opened and then a reverse movement in the lower ribs occurred. During inspiration the entire costal margins and hypochondria of both sides were drawn toward the median line. The abdominal wound was then clamped and the former inspiratory widening of the subcostal angle occurred. This observation was repeated a number of times until it was clearly apparent that removal of the viscera was not necessary to convert the inspiratory widening of the subcostal angle to inspiratory narrowing of the angle. When the abdominal wound was closed we evidently had the same physical conditions as before the incision was made.

The dog's diaphragm is more convex than the human diaphragm. The dog has thirteen ribs, and in some breeds of dogs, such as the setter, the thorax is particularly long, with a very acute subcostal angle. Such a conformation gives a high dome to the diaphragm, so that when the intercostal muscles are paralyzed, the subcostal angle widens during inspiration, because there is such a great disparity between the resultant line of traction of the diaphragm and the anatomic line of the diaphragm. The resultant line of traction is a straight line drawn from the central tendon to the costal margins where the

diaphragm is inserted. When the abdomen is closed, the respiratory descent of the diaphragm is attended with an increase in intra-abdominal pressure which is transmitted equally in all directions. If the lateral pressure in the abdominal cavity produced by descent of the diaphragm exceeds traction on the costal margins, then the hypochondria will spread during inspiration, although the intercostal muscles may be paralyzed. When there is an opening in the epigastrium, then descent of the diaphragm simply displaces the air and does not increase the intra-abdominal pressure; consequently there is no pressure to counterbalance the traction on the costal margins and the entire costal margin is drawn toward the median line. It will be observed also, that when the intercostal muscles were paralyzed in this particular dog, only the ninth, tenth, eleventh and twelfth ribs moved outward; the sixth, seventh and eighth ribs were stationary. This was due to the varying curve of the diaphragm in its different parts. The anterolateral portion of the diaphragm has less convexity than those fibers in the lateral portion which are inserted in the lower ribs. Consequently, the less disparity there is between the curve of the fibers and the straight line of resultant traction, the more advantage will traction acquire over any force which tends to move the costal ends or ribs away from the median line.

This was proved by repeating the experiment on a dog of the bulldog type, which has a shorter thorax and less acute subcostal angle than in the dog used in the experiment just described. When the intercostal muscles were paralyzed by section of the dorsal spinal cord at the fourth dorsal segment, all the intercostal muscles below this level were paralyzed, but unlike the previous experiment, the entire costal margins on both sides were drawn toward the median line. The movement of the costal margins was unchanged by opening the abdomen. In this manner I believe we can account for the time honored experiments of Duchenne, and also for the differing results obtained by his predecessors. Duchenne evidently used dogs with a high arch to the diaphragm, and so did Beau and Maissiat, but de Brou, in his experiment, employed a dog with less convexity of the diaphragm and observed both costal margins drawn toward the median line during inspiration. Thus it seems that finally we have a satisfactory explanation for the conflicting results obtained by different experimenters who have studied the function of the diaphragm.

I have never seen an instance of paralysis of the intercostal muscles in man which was attended with inspiratory widening of the subcostal angle and spreading of the hypochondria. This is due to the fact that the dome of the diaphragm is not sufficiently arched to permit the inspiratory increase of pressure within the abdomen to exceed the diaphragmatic traction on the costal borders during inspiration.

The significance of the arch of the diaphragm for inspiratory movements of the costal margins was fully discussed in a publication by me³ in 1913. Since that time there has been gathered much confirmatory evidence.

I have had three experiences which prove the correctness of the idea that the true explanation lies in the disparity between the resultant line of traction and the curve of the diaphragm, and not in the height of the diaphragm. If the curve of the diaphragm is responsible for the outward movement of the costal borders during inspiration, then it is obvious that the costal margin should diverge from the median line when the diaphragm is convex on its under surface as well as when it is convex on its upper surface.

This was observed to be a fact in two cases of thoracic empyema of the left side in which the normal spleen was displaced below the costal border by the downward displacement of the diaphragm. In both cases there was inspiratory divergence from the median line by the left costal border. One quart of pus was then aspirated and then the left costal margin was drawn toward the median line during inspiration. Later, two quarts more of pus were aspirated, whereupon the left costal margin diverged from the median line. When the line of traction and the plane of the diaphragm coincided, that is, when the diaphragm was arched neither upward nor downward, then the acting diaphragm gained the mastery over the costal border against the antagonists, namely, the intercostal muscles. When the diaphragm was arched either upward or downward, then there was sufficient disparity between the resultant line of traction of the diaphragm and the plane of the diaphragm so that the diaphragm's antagonists (the intercostal muscles) gained the mastery of the costal margin and the rib margin moved away from the median line during inspiration.

These cases also prove the incorrectness of the idea of the piston descent of the diaphragm during inspiration being the cause of the inspiratory spread of the hypochondria. When the left diaphragm was convex on its under surface its contraction caused a lengthening of the abdominal cavity instead of the normal shortening, so there could have been no inspiratory increase of the intra-abdominal pressure from activation of the left diaphragm. In spite of this fact, the costal margin moved away from the median line during inspiration just as when the diaphragm was convex on its upper surface.

There are other reasons to prove that in man the piston-like descent of the diaphragm is not a factor in the inspiratory widening of the subcostal angle. The curves of different groups of fibers in the diaphragm vary greatly. There is much less curving of the fibers which pass from the central tendon of the diaphragm to the costal margin near the median line than there is in those fibers which pass from the

central tendon to the costal border in the axillary line. We see the line of the diaphragm at its sternal portion more nearly approaches a straight line than at any other part. The anterolateral part of the diaphragm requires less depression to give this part of the diaphragm a horizontal position than is required to accomplish the same for parts occupying a more lateral position. The anterolateral part of the diaphragm has a slight curve to its fibers from origin to insertion; it is very near the critical position, so that very slight depression is required to give this portion of the diaphragm the mastery over that portion of the costal margin where it is inserted.

When the heart or pericardial sac is enlarged to a moderate degree, that part of the costal margin from the median line to the ninth costal cartilage will be drawn toward the median line during inspiration; but beyond this median half of the costal margin, the inspiratory movement is in a lateral direction. On several cases I have observed the reverse of this when the posterolateral portion of the pleural sinus was filled with fluid. The subcostal angle widened during inspiration, but the lower and lateral portion of the costal border was retracted.

When the entire lung is emphysematous to a sufficient degree to cause retraction of any portion of the costal margin, the entire margin is retracted. Under these conditions there is inspiratory narrowing of the subcostal angle and inspiratory retraction of the whole of both costal borders.

In my former communication the importance of this sign was pointed out as the only method of estimating the higher degrees of emphysema. Moderate emphysema of the pulmonary borders may fill the pleural sinuses so that lung resonance will descend to the bottom of the pleural sinus in the anterior, lateral and posterior lines, but if the great body of the lung is not emphysematous, there will be no inspiratory narrowing of the subcostal angle. For example, a patient with chronic bronchitis and emphysema will have the lower borders of the lungs at the eighth, tenth and eleventh ribs, respectively, in the anterior, axillary and scapular lines, and have no respiratory discomfort or inspiratory retraction of any part of the costal margins; on the following day the man may have cyanosis and dyspnea with a rise of 2 per cent. in the carbon dioxid concentration of the alveolar air. The percussion borders of the lungs are unchanged, but the body of the lung is much larger, and the only physical sign of this enlargement will be inspiratory narrowing of the subcostal angle and inspiratory retraction of the entire costal margin of both sides.

Furthermore, this differentiation between depression of the anterolateral portion alone of the diaphragm from depression of the entire diaphragm is important in estimating the pulmonary and cardiac sources of air hunger. It is not at all uncommon to see patients with

moderate emphysema whose hearts are enlarged. The percussion borders of the lung may reach to the bottom of the pleural sinuses, but if there is only inspiratory narrowing of the subcostal angle, and the costal margins below the ninth costal cartilages move laterally during inspiration, then the patient's air hunger is not due to emphysema, for when air hunger from emphysema exists there will be not only inspiratory narrowing of the subcostal angle, but there will be inspiratory retraction of the entire costal margin.

A careful study of the subcostal angle is also important to determine the symmetry or asymmetry of movement of the two costal margins in their upper or median portions.

If the patient should have enlargement of the left ventricle alone, as in cases of arterial and aortic valve disease, then the median portion of the left costal margin will be retracted or move less in an outward direction during inspiration than the symmetrical part on the right.

In cases of mitral stenosis, myocardial disease, and enlargement of the pericardial sac there will be symmetrical narrowing or constraint of the subcostal angle during inspiration if the anterolateral portion of the diaphragm is depressed beyond the critical point. These points are all specifically mentioned because I have found that an analysis of the respiratory movements of the subcostal angle and costal borders has been of much service in arriving at an estimate of the relative enlargement of the two sides of the heart, enlargement of the pericardial sac and enlargement of the entire body of the lungs.

In a routine examination it is important to determine the symmetry or asymmetry of movement in the subcostal angle and lower costal margins and the relation of their movements to the median line. When the arch of the diaphragm is accentuated, as in cases of hepatic enlargement or subphrenic accumulations of pus or serum, then the outward movement of the costal border on the affected side is increased. Accentuation of the diaphragmatic arch and fixation of the diaphragm to the thoracic wall were discussed in a former article;³ so I shall refrain from discussing this phase of diaphragmatic action any further than to describe a single experience of recent date in which the balance between the intercostal muscles and diaphragm was clearly illustrated. The patient had an acute suppurative pyelophlebitis which produced a moderate enlargement of the liver in an upward direction. The patient had violent and protracted hiccough in which the diaphragm and intercostals were both activated. On the left side the costal margin was drawn toward the median line with each hiccough; on the right side the costal margin moved away from the median line with each hiccough. At the necropsy nothing was found to account for this asymmetry of

movement of the costal margins excepting a very moderate enlargement of the liver in an upward direction.

In studying the respiratory movements of the base of the thorax we must differentiate between evidences of phrenic activation and phrenic excursion.

The Litten diaphragm phenomenon is an evidence of phrenic excursion and is a supraphrenic phenomenon which is present only under normal conditions, or conditions which approximate the normal. The sign is not present under abnormal conditions.

The direction of movement and comparative movements of the median and lateral portions of the costal margins on the two sides give us valuable information on activation of the diaphragm and the position of its median and lateral parts. The direction in which any portion of the costal margin may move is determined by the resultant of two forces. One is the expression of the action of the intercostal muscles, which always widens the subcostal angle and spreads the hypochondria; the other force originates in activation of the diaphragm and always draws the costal margin toward the median line. When the resultant of these two forces causes narrowing of the subcostal angle, the subcardial or median portion of the diaphragm is less convex than normal. When the entire costal margin is drawn toward the median line, the entire phrenic leaf has lost a large part of its convexity. The movement of the costal margins has nothing to do with excursion of the diaphragm; it is merely the resultant of activation of the intercostal muscles and of the diaphragm. The only subphrenic sign of phrenic excursion is protrusion of the epigastrium and lateral portions of the abdomen.

The significance of the slight arch of the anterolateral portions of the diaphragm is illustrated very nicely in cases of acute cardiac dilatation due to myocardial incompetence from arterial sclerosis. It is a common experience to see these patients brought to the hospital with dilatation of both sides of the heart. During this period there will be symmetrical inspiratory narrowing of the subcostal angle, but the lower and lateral portions of the costal margins move away from the median line during inspiration. As the heart recovers from its acute dilatation, the upper and inner half of the right costal margin will resume its outward movement during inspiration, but the left side of the subcostal angle will be restrained in its outward movement or may continue to move toward the median line during inspiration. This is, of course, due to the fact that the left ventricle is permanently enlarged and depresses the left sternocostal portion of the diaphragm. The symmetry and asymmetry of movement of the two sides of the subcostal angle and the lower and outer halves of the costal margins give

much valuable information concerning the total volume of the lungs, and form and size of the heart and heart's sac. Furthermore, an exact analysis of the respiratory movement of each part of the thoracic cage is essential to form an adequate estimate of the ventilatory function of the different parts of the lungs. Such an analysis is also necessary to form an exact idea about the factors in supraphrenic and infraphrenic diseases which may modify the curve in any part of the diaphragm.

702 Rose Building.

SERUM CHANGES FOLLOWING PROTEIN "SHOCK" THERAPY *

WILLIAM F. PETERSEN, M.D.

CHICAGO

The degree of interest with which certain phases of therapeutics along nonspecific lines has been received would seem to indicate that clinical observation of such character must have been quite frequently, although the possible significance had escaped comment. Various German clinicians have, in recent times, emphasized the striking therapeutic effects achieved with this so-called "protein" therapy, a not inapt designation, conveying, as it does, not only the concept of the basic reacting agent, but implying, too, wide range of effectiveness as a therapeutic measure. The best results have undoubtedly been obtained in the arthritic processes, an extended series of observations on such cases having been published by Miller and Lusk,¹ and Culver.² They seem particularly favorable for treatment, because the contraindications are few and the objective and subjective evidence of improvement under treatment are directly observable.

In a paper published last year Jobling³ discussed some of the factors that were possibly operative following intravenous protein therapy, basing his views on an extended study in experimental animals. The changes in the blood pressure and the blood cytology have been studied by Scully⁴ in Miller's Clinic, and inasmuch as Culver⁵ has followed the changes in antibody formation, these phases are not covered in this paper, which is limited to the study of certain ferment and physical alterations following protein injections.

When the normal or diseased organism is subjected to a protein shock of whatsoever origin — bacterial, protein split products, milk, etc. — certain fundamental but as yet intangible alterations occur in the organism, as a result of which an increased resistance to infection

* Submitted for publication June 25, 1917.

* From the Medical Clinic of Joseph L. Miller at the Cook County Hospital and the Laboratory of Physiologic Chemistry, College of Medicine University of Illinois.

1. Miller, J. L., and Lusk, F.: The Use of Foreign Protein in the Treatment of Arthritis, *Jour. Am. Med. Assn.*, 1916, **67**, 2010.

2. Culver, H.: The Treatment of Gonorrheal Infections, *Jour. Am. Med. Assn.*, 1917, **68**, 362.

3. Jobling, J. W., and Petersen, W. F.: The Nonspecific Factors in the Treatment of Disease, *Jour. Am. Med. Assn.*, 1916, **66**, 1753.

4. Scully, F. J.: *Jour. Am. Med. Assn.*, 1917, **69**, 20.

5. Culver, H.: *Jour. Lab. and Clin. Med.*, October, 1917, **2**.

and to intoxication is definitely established. The terms "antianaphylaxis" and "desensitization" applied to this state convey certain ideas of specificity and are therefore not quite suited; the German "unstim-mung" possibly expresses the fundamental character of the changes involved, and von Groer⁶ has coined the term "ergotropie" to cover the new therapeutic conception whereby we seek to change the reactivity of the host through a biologic reaction rather than directly to alter or destroy the invading parasite.

In its essentials, the state of antianaphylaxis, or the refractory period following anaphylactic shock, is found to occur after all varieties of protein shock. Vaughan⁷ noted this resistance following the injection of his protein split products; Zinsser and Dwyer⁸ have discussed it in its relation to proteophylatoxin or anaphylatoxin; Jobling⁹ observed it to occur after serotoxin injections and Tigue and McWilliams¹⁰ have recently observed the increased resistance to typhoid infection in rabbits after a typhoid vaccine shock. It has been known for some time, of course, that antianaphylaxis is relatively nonspecific, insofar as following recovery from a nonfatal shock dose in a doubly sensitized animal the sensitization to the second antigen is greatly reduced. Bessau¹¹ and his associates have fully discussed this subject. Inasmuch as the "ergotropie" observed in these newer therapeutic studies is also nonspecific, its relation to the antianaphylactic condition is at least made probable.

In a series of studies made some time ago, Jobling¹² and his associates found that anaphylactic shock (and the protein intoxications in general) was accompanied in dogs by marked changes in the blood ferment-antiferment balance. It seemed warranted to assume that, at least in such animals, the shock involved both cellular and humoral factors; that the cellular reaction was probably the primary one, and that the serum reactions that followed brought about further intoxication and death. It was observed that during shock a condition obtained (low antiferment and increased protease) when proteolytic activity was favored, while following shock the reverse held true (increased antiferment and low protease). During this refractory period reinjection is followed by no change in the ferment-antiferment balance. Rusznjak¹³ was the first to observe the change in the antiferment, and

6. von Groer: München. med. Wchnschr., 1915, **62**, 1312.

7. Vaughan, V. C.: Protein Split Products, 1913, Lea & Febiger, Philadelphia and New York.

8. Zinsser, H., and Dwyer, J. A.: Jour. Exper. Med., 1914, **20**, 387.

9. Jobling and Petersen: Jour. Exper. Med., 1914, **19**, 480.

10. Tigue, O., and McWilliams, H.: Jour. Immunol., 1917, **2**, 167.

11. Bessau, G., Opitz and Preusse, O.: Zentralbl. f. Bakt., Part 1, Orig., 1914, **74**, 162 and 310.

12. Jobling, Petersen and Eggstein: Jour. Exper. Med., 1915, **22**, 401.

13. Rusznjak, S.: Deutsch. med. Wchnschr., 1912, **38**, 168.

suggested its possible significance in the phenomena of resistance following shock.

Friedberger and his school have developed the ideas originally presented by Matthes, and by Vaughan in this country, concerning the relation of fever to protein intoxication. According to this conception, which is based on a vast accumulation of experimental evidence, the invading organisms themselves, unless they happen to excrete a definite toxin, cause no marked intoxication of the host until the host becomes sensitized to the bacterial protein derived from disintegrated organisms. This state is ushered in by the febrile reaction. Freedom from symptoms could then occur either (*a*) when the host is desensitized, or (*b*) when the parasites are destroyed; it is clear that the first supposition need not imply the destruction of the infecting organisms. Unfortunately, in this relatively simple conception another factor is manifest, namely, that from the bacteria are derived not only native proteins that sensitize the host, but protein split products as well, which are able to intoxicate the host directly. During the refractory period the resistance to these is also increased, but the chief agent in ridding the system of this poison would be proteolytic ferments of the peptidase or ereptase type, which would hydrolyze these toxic products to the lowest and nontoxic form. From these considerations it is apparent that if in typhoid fever, for instance, protein shock is induced and the disease terminated by crisis, the infecting organism need not be destroyed, the host may be simply desensitized so that the condition in a manner resembles the period of incubation during which time organisms may be abundantly present, but cause no reaction. That this is actually the case is indicated in several reports from German workers who have obtained positive blood cultures and stool cultures in typhoids a considerable period of time after all disease manifestations had subsided following intravenous shock therapy; the patients being afebrile, the spleen small and the diazo reaction negative.

With these considerations in mind, it would seem pertinent to ascertain just what changes do occur in the serum of patients following protein therapy and in how far such changes may account for the therapeutic benefit derived.

EXPERIMENTAL

The serum changes studied included the following:

- (*a*) Stalagmometric
- (*b*) Concentration of serum (total nitrogen)
- (*c*) Noncolloidal nitrogen of serum
- (*d*) Anti ferment
- (*e*) Serum protease. (Chloroform method at 47 C.)
- (*f*) Serum ereptase. (Peptone splitting at 47 C.,
tryptophan reaction)
- (*g*) Serum diastase (Wohlgemuth method)
- (*h*) Serum esterase (Michaelis-Rona and ethyl butyrate
methods)

The proteins injected were either typhoid bacilli in doses varying from 25 to 150 million (fresh vaccine) or albumoses; primary and secondary proteoses fractionated from Witte peptone. The latter, in doses from 40 to 60 mg. give a satisfactory reaction. The protocols selected are representative of the changes observed in a large series of cases.

(a) As a result of the peripheral vasodilation and the profuse sweating that normally follows protein shock, appreciable changes occur in the concentration of the blood serum, which in turn is reflected in the rate of the flow through the stalagmometer, as shown in the following determination:

J. P. Monarticular rheumatism. Typhoid vaccine injection.

Rate of flow before injection.....	12.8 drops per minute
Rate of flow 2 hours after injection...	12.0 drops per minute
Rate of flow 8 hours after injection...	11.4 drops per minute
Rate of flow 24 hours after injection...	10.6 drops per minute
Rate of flow 72 hours after injection...	11.3 drops per minute

(b) The concentration of the serum proteins is increased following the injections; for comparison the corresponding stalagmometric readings are shown together with the Kjeldahl titration for 2 c.c. of serum.

J. B. Acute arthritis. Typhoid vaccine injection.

Stalagmometric Readings		Fifth Normal Hydrochloric Acid, Kjeldahl Titration for 2 C.c. Serum	
Before injection	10.7 drops	6.2	c.c.
3 hours after injection....	10.0 drops	6.27	c.c.
6 hours after injection....	9.3 drops	6.5	c.c.
18 hours after injection....	9.2 drops	6.975	c.c.

The change in the stalagmometer readings must depend largely in this case on the alteration of the concentration of the serum which may be of sufficient magnitude to mask smaller changes that might be expected to result from changes due to alterations of the dispersion of the serum colloids.

(c) The nonprotein nitrogen of the serum remains practically unaltered, as shown in the following two cases:

H. L. Acute arthritis and pharyngitis. R. C. Acute arthritis, with possible endocarditis; both received typhoid vaccine intravenously.

	H. L. Mg. Per C.c.	R. C. Mg. Per C.c.
Blood before injection.....	0.5	0.47
Blood 3 hours after injection.....	0.5	0.45
Blood 18 hours after injection.....	0.55	0.47
Blood 72 hours after injection.....	0.5	0.47

It is evident that no retention of nonprotein nitrogen takes place as a result of possible injury to the cells of the excretory apparatus, which coincides with the urinary examination made on cases following protein shock; that is, no albuminuria occurred unless already present before the injections and in these cases no increase in the amount of albumin was noted.

(d) The changes in the antiferment of the blood serum are usually well marked and quite uniform in the cases that react favorably to the shock therapy. Chart 1, A illustrates the changes taking place for a three-day period of observation in a case with complete recovery from an acute arthritis following intravenous injection of 60 mg. of a primary proteose. The persistence of the increased antiferment titer may be much less in duration, as shown in the second Chart 1. B. This case, K. H., was one of multiple subacute arthritis which did not improve to any marked extent after injection of typhoid vaccines, although there was temporary relief.

Finally, the cases that show no permanent improvement seldom show any increase in the anti-ferment, indeed almost always present a decrease in the titer following the shock, as illustrated in the third and fourth charts, 1, C and 1, D.

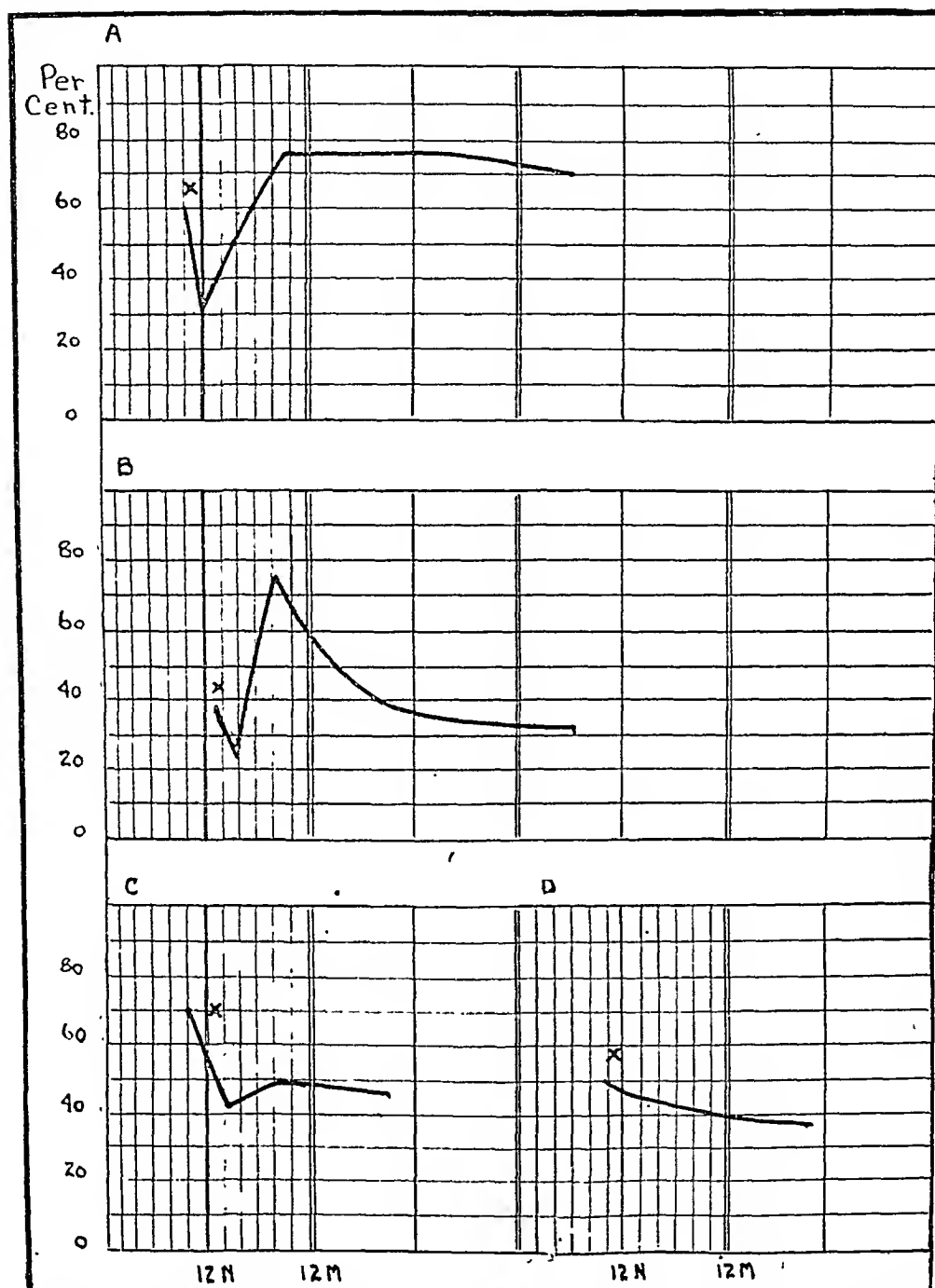


Fig. 1.—Changes in anti-ferment titer following protein shock. X indicates injection.

(e) The serum protease is almost invariably decreased immediately following the shock, but later increases progressively for a period of two or three days, as shown in the following tabulations in which the titer of the ferment

is expressed in the amount of serum protein digested in 1 c.c. at 47 C. when emulsified with chloroform. The titer for the first eighteen hours following injection in an acute arthritis, G. W., with complete recovery, was as follows:

Before injection.....	0.08 mg. per c.c.
2 hours after injection.....	0.02 mg. per c.c.
6 hours after injection.....	0.07 mg. per c.c.
18 hours after injection.....	0.06 mg. per c.c.

H. L. Acute arthritis; typhoid vaccine.

Protease before injection.....	None demonstrable
Protease 3 hours after injection.....	None demonstrable
Protease 18 hours after injection.....	0.03 mg. per c.c.
Protease 48 hours after injection.....	0.2 mg. per c.c.

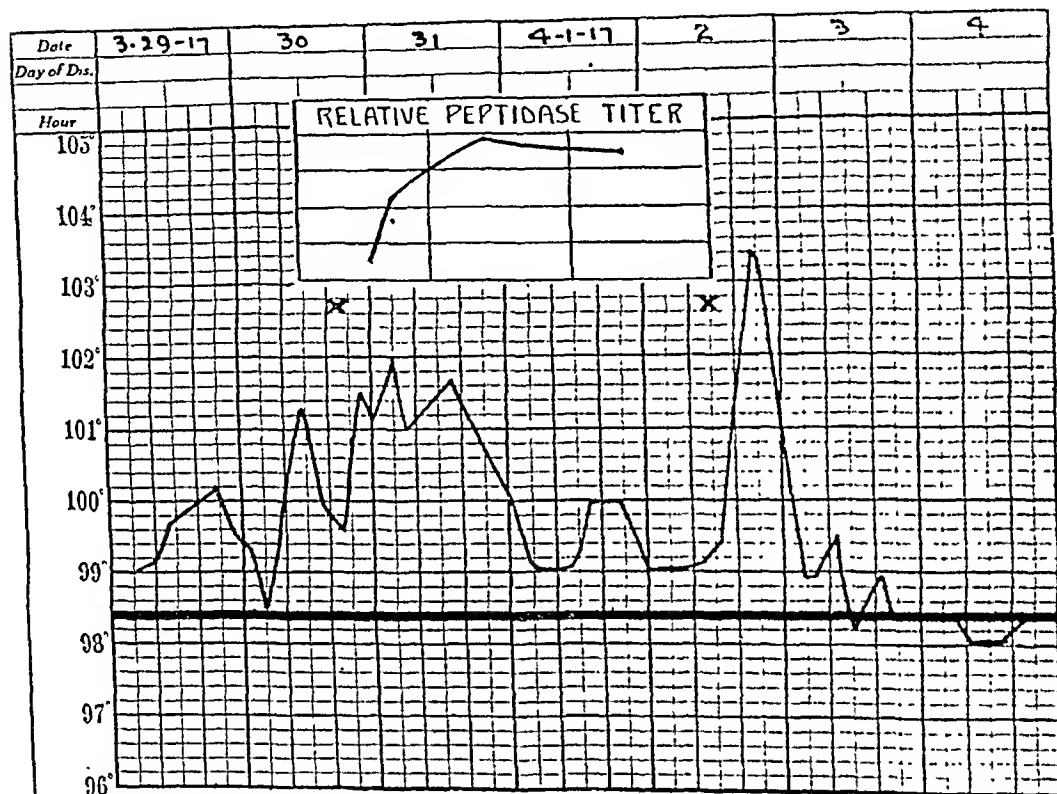


Chart 2.—Peptidase titer following protein shock. X indicates injection.

(f) The serum ereptase or peptidase is almost invariably increased in those cases that respond to vaccines with clinical improvement, the maximum concentration being reached after twenty-four hours.

J. C., white man, with physical findings of diffuse bronchitis, had persistent irregular temperature for the two weeks he was under observation, with no signs of improvement. Two doses of typhoid vaccine were given intravenously, following which marked clinical improvement occurred, together with clearing of physical findings and an afebrile temperature curve. The relative peptidase titer observed in the serum following the second dose of vaccine is illustrated in Chart 2.

A. G. Multiple acute arthritis. Typhoid vaccine was administered, with complete recovery. The peptidase titer in this case was as follows:

	Serum			
	0.5 C.c.	0.25 C.c.	0.125 C.c.	0.0625 C.c.
Before injection	+++	+++	+	—
6 hours after injection.....	++++	++++	+	—
24 hours after injection....	++++	++++	++	+

The majority of cases that show no clinical improvement give no evidence of an increase in peptidase; this is illustrated in the following patient:

J. S. Gonorrheal rheumatism (knees and ankles) of several months' duration, with subacute prostatitis. Three c.c. 2 per cent. proteose was injected, resulting in well marked reaction but no clinical improvement.

	Serum	
	0.5 C.c.	0.25 C.c.
Peptidase titer before injection.....	+	+
After twenty-four hours.....	+	—

There being no clinical improvement, the patient was given three injections of typhoid vaccine without benefit. Gonococcus vaccine was then tried, without effect. The patient was relieved to a greater extent by iodids given intravenously than with any other measure, but did not make a complete recovery until he had developed an intercurrent peritonsillar abscess, following which the joint symptoms cleared completely.

(g) Diastatic activity. This ferment is almost invariably diminished after the shock and the titer may remain low for several days thereafter.

J. P. Monarticular arthritis.

Diastatic titer before injection.....	$D_{24}^{37^\circ} = 32$
3 hours after injection.....	$D = 16$
6 hours after injection.....	$D = 16$
18 hours after injection.....	$D = 8$

(h) The study of the lipolytic activity (esterase titer) revealed no consistent alterations.

RESISTANCE TO REINJECTION

When the patient is subjected to two or more doses of vaccine intravenously, evidences of resistance are occasionally noted, not only against the shock effect—chill, fever and sweating—but also to some extent against further beneficial effect. It is our impression that the maximum benefit to the patient follows the first injection, although undoubtedly a number of cases will show continued improvement with reinjections when the primary injection did not completely clear up the disease. The resistance which develops is nonspecific in character, as illustrated in the following case:

C. H. Acute multiple arthritis. He received at intervals three doses of typhoid vaccine, each from fifty to seventy-five million, intravenously. The patient was improved, but still complained of some stiffness of the ankles. At this time it was observed that the injection of a dose of the same amount was followed by no reaction. The serum examination made at this time showed a relatively high antiferment titer—0.01 c.c. of serum inhibiting 80 per cent. of the trypsin unit; ereptase was present in a moderate amount, 0.125 c.c. serum giving a good tryptophan reaction in twenty-four hours' digestion at 47 C.; and the serum contained protease—0.08 mg. digestion per cubic centimeter in twenty-four hours at 47 C. These changes, while definite, were, however, identical with those observed in cases not resistant to reinjection; so that we are forced to conclude that the resistance must be largely cellular in character.

DISCUSSION

From the observations described it is evident that the reaction of the host which follows protein shock therapy is accompanied by definite serum changes, including a mobilization of both protease and ereptase,

alterations in the antiferment titer, as well as certain physical changes. It is to be emphasized that these changes are not to be considered as wholly responsible for the therapeutic effect observed following shock therapy; indeed, we are under the impression that they should be regarded rather as an index of cellular changes which are the primary ones concerned; but inasmuch as the means of investigation of direct cellular changes are limited, the serum changes may be considered as offering at least some tangible object for study. Culver has recently followed the antibody changes following intravenous vaccine therapy. He finds an increase in the specific bacteriolysin and opsonin (gonococcus) following injections of gonococcus vaccines (as well as proteoses), an increase most marked after the first injection; with subsequent injections a decrease may be observed, despite continued improvement of the patient. Practically the same may be said of the proteolytic serum ferments. A mobilization takes place after the injection, but following injections may be followed by no such change. On the other hand, the cases that do not show clinical improvement seldom show an increase in peptidase, thus differing from the antibody observations. The ereptase may be considered a detoxicating agent which aids in the elimination of the toxic products of the pathogenic organism, while the antibody mobilization may be responsible for the actual destruction of these organisms.

The mobilization of the ferments is much less prompt than in experimental animals, nor is it directly proportional to the severity of the chill or the degree of the temperature reaction, although as a rule the clinical improvement is more apparent when a good febrile reaction is elicited.

It is of course well known that the thorough sweating of a patient will of itself afford marked relief of arthritic symptoms, but relief is practically always transient. It is probable that the immediate relief which follows shock therapy in these cases is due to a similar cause, the difference lying in the permanency of the cure. It is reasonable to suppose that in this the mobilization of the leukocytes and antibodies and ferments is of importance.

The changes in the antiferment have been discussed previously; following the initial decrease a rise takes place which in the favorable cases persists for from two to seven days, while in the cases that show no clinical improvement the increase has been found to be transient or to be lacking altogether.

As will be discussed in a following paper, an increased antiferment titer is commonly associated with an increased resistance to protein intoxication, the increase either itself protecting the cells or at least being indicative of cellular changes associated with an increased resist-

ance. Whether there exists a possible direct relation to bacterial proliferation is a question that has not as yet been thoroughly studied. Wright¹⁴ has carried out some experiments along this line, but his investigations were concerned chiefly with the bacterial flora of wounds and the relation of the leukoproteolytic ferments and antiferment thereto.

Tigue and McWilliams¹⁵ have suggested that the therapeutic effect may depend on an increased passage of antibody containing serum into the lymph channels. In experimental animals Davis and I¹⁶ have, indeed, found that a marked augmentation of the flow from the thoracic duct does occur following shock, so that the suggestion is one that may have considerable bearing on the subject.

We believe it is at present justifiable to consider that the benefits of shock therapy do not depend on any single alteration in the reacting organism, but on a series of factors in which not only the serum antibody and ferment changes, but the leukocytosis, the fever and sweating and the increased lymph flow have a part along with the important cellular changes which are as yet intangible.

14. Wright, A.: *Brit. Med. Jour.*, 1915, **2**, 629.

15. Tigie and McWilliams: *Jour. Immunol.*, 1917, **2**, 193.

16. Davis, B. F., and Petersen, W. F.: *Jour. Exper. Med.*, 1917, **26**.

VENTRICULAR FIBRILLATION IN MAN WITH CARDIAC RECOVERY *

G. CANBY ROBINSON, M.D., AND J. F. BREDECK, M.D.
ST. LOUIS

The interest in ventricular fibrillation as a disturbance of the cardiac activity of man has been centered about the rôle this phenomenon may play in causing sudden death. It has been generally accepted that when the human ventricles pass into a state of fibrillation, death is an almost immediate and invariable consequence.

Ventricular fibrillation can be determined definitely by electrocardiograms, as its presence is indicated by a well defined type of record. This type has been frequently obtained from animals in which ventricular fibrillation was directly observed in the exposed heart. The usual waves that are produced by the passage of the excitation impulse through the ventricles and the resulting contraction disappear and in their place rapidly recurring, more or less irregular, waves occur following each other so closely that no period of cardiac inactivity is indicated. The waves vary in height and in form, and short stretches during which they are of diminished size are apt to occur at intervals in the records.

Although ventricular fibrillation may be a frequent cause of sudden death of man, very few electrocardiographic records have been obtained which signify its presence, because it is necessarily transient, as it is in most instances incompatible with life. Records obtained by one of us¹ from seven patients at the time of death from various causes indicated that fibrillation of the ventricles preceded briefly complete cardiac arrest in one and possibly two instances. A characteristic record of ventricular fibrillation was also obtained by Halsey² in one case at the time of death, while Hoffman³ has published a record which he interprets as indicating the brief occurrence of ventricular fibrillation ter-

* Submitted for publication May 17, 1917.

* From the Department of Internal Medicine, Washington University Medical School.

* Read at the meeting of the Association of American Physicians, May 2, 1917.

1. Robinson: A Study with the Electrocardiograph of the Mode of Death of the Human Heart, *Jour. Exp. Med.*, 1912, **16**, 291.

2. Halsey: A Case of Ventricular Fibrillation, *Heart*, 1915, **6**, 67.

3. Hoffman: Fibrillation of the Ventricles at the End of an Attack of Paroxysmal Tachycardia in Man, *Heart*, 1912, **3**, 213.

minating in recovery at the end of an attack of paroxysmal tachycardia. His interpretation is questioned by Lewis,⁴ and Hart⁵ and others.

These few records constitute the entire direct evidence that ventricular fibrillation occurs in man. The belief of its occurrence beyond this evidence is based on conjecture and analogy with experimental results. The question of its occurrence and its importance as a cause of sudden death has been discussed by Lewis⁴ who says that he has the strongest *a priori* grounds for the belief that sudden death results from ventricular fibrillation in many patients. He points out that when



Fig. 1.—Three usual leads, obtained on day of admission, Dec. 29, 1915.

the ventricles fibrillate, the coordinate beat of these chambers is lost; the muscle is divided up into small areas, which show independent activities. This type of activity is functionally entirely ineffectual and the cardiac output ceases, the blood pressure falls to zero and the circulation comes to a standstill.

The observations to be reported here were made on a patient who had a series of attacks of prolonged cardiac syncope, closely resembling Stokes-Adams syndrome, from which she recovered. An electrocar-

4. Lewis: Observations on Cardiac Syncope, Lectures on the Heart, New York, 1915, p. 113.

5. Hart: The Diagnosis and Treatment of Abnormalities of Myocardial Function, New York, 1917, p. 171.

diagram obtained during one of these attacks is typical of ventricular fibrillation, and it seems likely that all syncopal attacks were of the same nature. This observation represents, therefore, recovery from at least one relatively prolonged period of ventricular fibrillation, and probably recovery from several such periods.

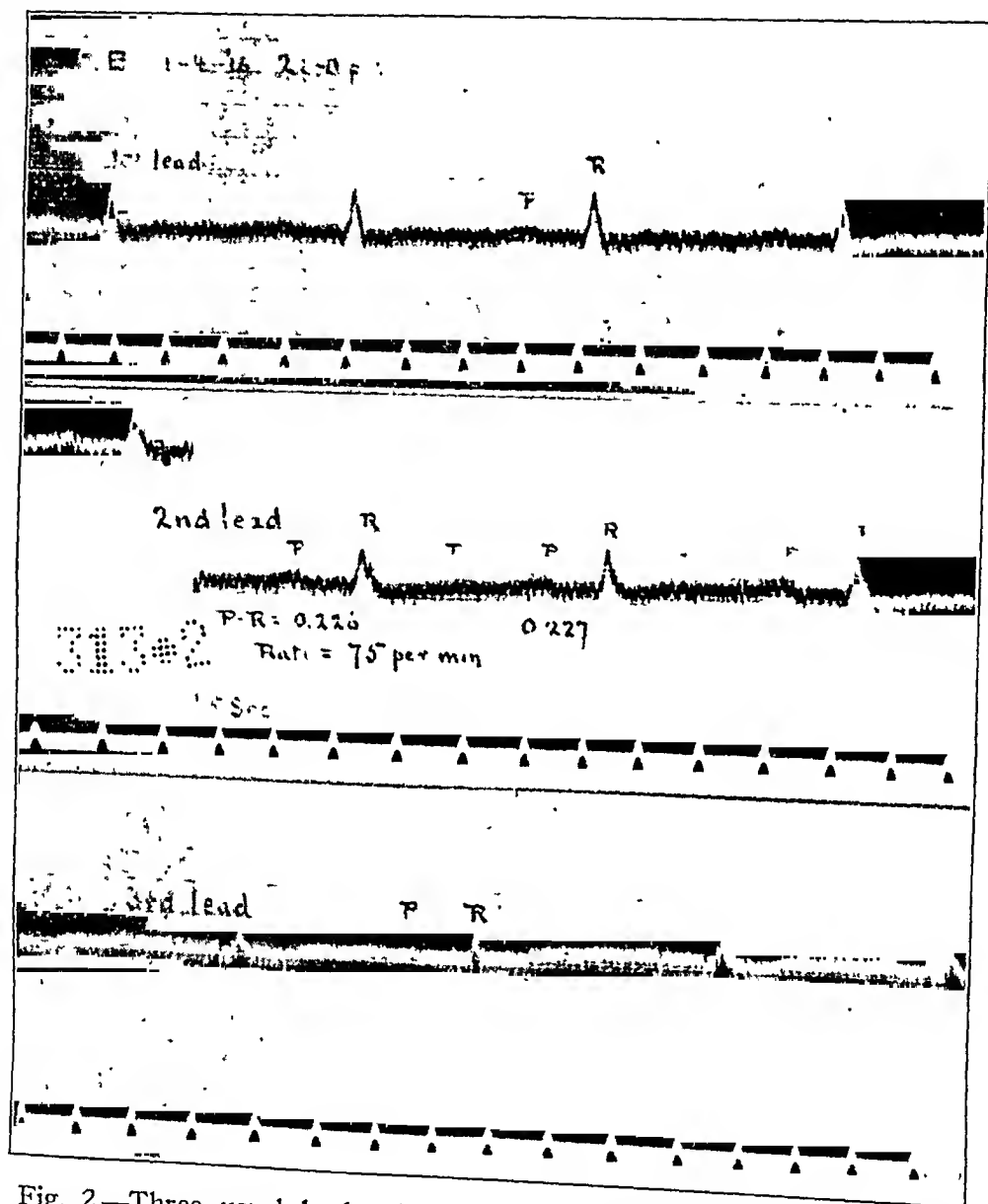


Fig. 2.—Three usual leads, Jan. 4, 1916. Eight minutes before onset of ventricular fibrillation.

REPORT OF CASE

History.—F. B., a woman aged 45, was admitted to the Barnes Hospital, Dec. 29, 1915, complaining of shortness of breath, swelling of the feet, weakness and cough. The family history is irrelevant. She had had three attacks of rheumatism at the ages of 14, 20 and 30 years, and had chorea at 9 years. She had also had typhoid fever in childhood and scarlet fever at 20 years of age. During her first attack of rheumatism she was told her heart was affected. There was no history of a surgical operation, nor any evidence of syphilis.

She had been short of breath on exertion as long as she could remember, and had been very pale and "anemic" for fifteen years. Swelling of the feet had been present for about one month, during which time dyspnea became more marked. She had slept with her head elevated for many years, but had been coughing for only about three or four weeks. She had had polyuria for about a year.

Physical Examination.—Physical examination revealed a pale, fairly well nourished woman, who seemed in no great distress or danger. Slight cyanosis was observed. The heart was slightly enlarged. The apex beat was in the fifth interspace, 12 cm. to the left of the midsternal line. The cardiac dulness extended 3 cm. to the right and 13 cm. to the left of the midsternal line. There was a presystolic thrill over the apex as well as a presystolic and systolic murmur. The heart rate was 81 per minute and regular. Fine moist râles were heard over the bases of the lungs posteriorly. The liver was not palpable. A uterine tumor was present, and there was slight edema of the feet, legs and thighs. The systolic blood pressure was 138 mm. Hg, diastolic 72 mm. Hg. The blood examination showed 2,944,000 erythrocytes, and 29,200 leukocytes per cubic millimeter, and hemoglobin 30 per cent. (Sahli instrument). Albumin and casts were found in the urine. The excretion of phenolsulphone-phthalein amounted to 43 per cent. in two hours. During the first six days in the hospital the patient's condition improved somewhat and she seemed in a fairly satisfactory condition. The pulse ranged from 75 to 100 beats per minute. The temperature was slightly elevated at times, but gradually subsided. A blood culture remained sterile.

Subsequent Course.—Jan. 4, 1916, a pelvic examination was made per rectum. Shortly after the examination the patient was observed by the nurse to become suddenly unconscious "for a few minutes." She made jerking movements of her arms. The eyes were closed and the pulse was imperceptible. The intern, Dr. Fuson, was called immediately and when he arrived the pulse was weak and irregular. The patient was very blue and the feet were cold. The pulse became regular in a few minutes and beat fairly strongly at a rate of 68 per minute. The area of cardiac dulness was not increased. The presystolic and systolic murmurs were heard at the apex region as before. There was a hemorrhage in the conjunctiva of the left eye. The mental condition was clear and the patient was not suffering.

About one hour later, at 2:48 p. m., the patient was observed by the intern to become suddenly unconscious, when electrocardiograms were being taken. The pulse disappeared from the wrist, and the patient became very cyanotic. Breathing, except for occasional gasps, ceased for a period estimated at two or three minutes. The heart beat was inaudible at the apex.

The heart beat returned after being apparently absent for about four minutes, and in about fifteen minutes the heart was beating almost regularly at a rate of 85 to 100 per minute. During this time the breathing was slow, deep and snoring. The arms and feet were frequently stiffened out in convulsive-like movements. The reflexes of arms and legs were active. The pupils were pinpoint in size and there were irregular ocular movements.

At 5 p. m., two hours after the onset of unconsciousness, the patient became very noisy. She was still unconscious, but tossed her arms, head and feet about continually. She became quiet at 7 p. m., and at 8:30, although still unconscious, was breathing quietly, at times suggesting Cheyne-Stokes breathing. The pulse was irregular, about 80 per minute. The thrill could not be felt, and the heart sounds were very confusing to the ear.

At 11 p. m. the patient had her third convulsion. She became suddenly cyanotic and the heart-beat became inaudible. Breathing ceased for four minutes, the heart sounds disappearing before breathing stopped entirely. The breathing returned slowly, at first only 3 or 4 per minute, then gradually increasing up to 20 per minute. The heart beat returned very slowly, with

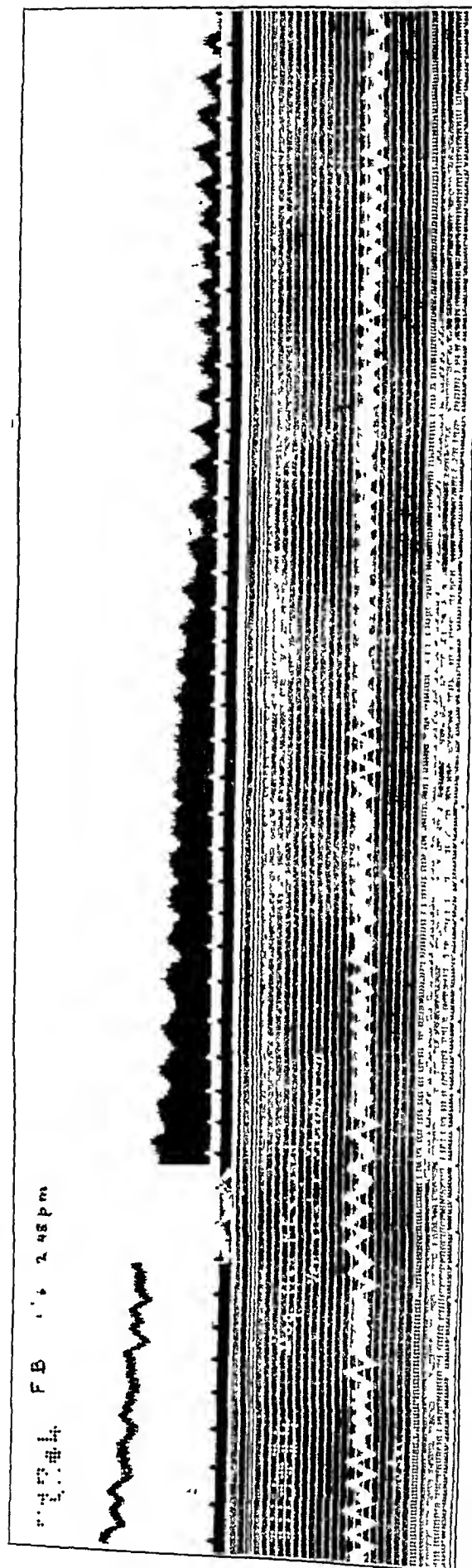


Fig. 3.—Upper curve. Record obtained during period of cardiac syncope at 2:48 p. m., Lead 2. Lower curve from dog. Ventricular fibrillation observed in the exposed heart. Lead from right fore leg and left hind leg.

an increasing rate. The heart rate in successive minutes was 27, 41, 35 and 45. The rate remained at about 56 per minute.

The following day, January 5, the patient was dazed but not delirious. She could answer questions intelligently, but was slow to recognize objects and people. The pulse remained very irregular and the heart sounds suggested myocardial weakness. Examination of the lungs and liver were negative. One mg. strophanthin was given at 9:50 a. m. At 2 p. m. fluid began to collect in the throat, which was expectorated with difficulty. Edema of the lungs developed and the patient died at 9:15 p. m., January 5, the heart remaining unchanged.

Electrocardiograms were made before, during and at frequent intervals after the second attack of unconsciousness. The records obtained on the day of admission (Fig. 1) show the normal cardiac mechanism, with complexes of the forms suggesting moderate left-sided predominance. They indicate no delay in the auriculoventricular conduction

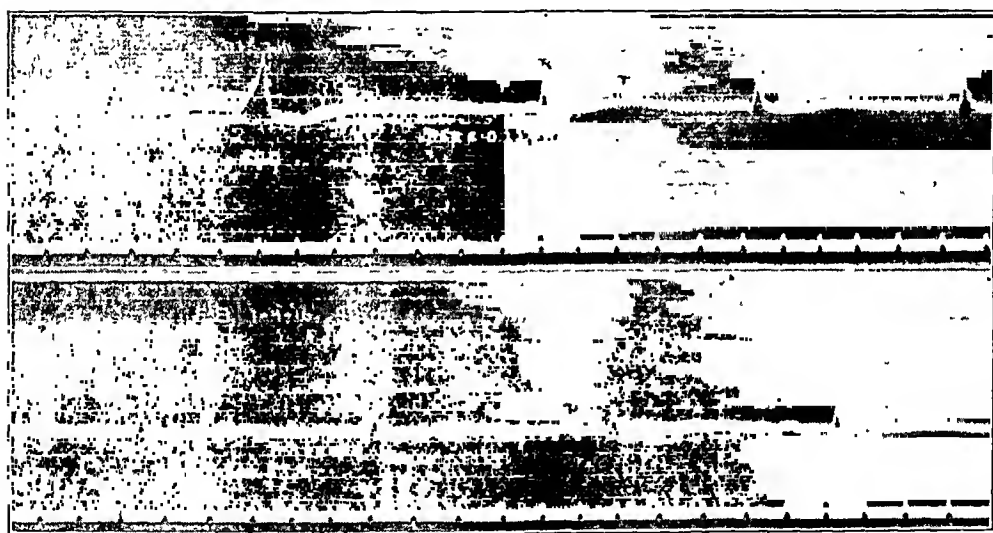


Fig. 4.—Curves obtained thirty minutes and seventy-two minutes, respectively, after the second period of ventricular fibrillation.

time. The heart rate was 100 per minute. The first record obtained on January 4, eight minutes before the second attack of unconsciousness, shows complexes nearly similar in form to those previously obtained, except that the A-V conduction time is now prolonged, the P-Q interval measuring 0.226 second (Fig. 2). The record obtained during the attack of unconsciousness at 2:48 p. m. is typical of ventricular fibrillation, as is shown by the curve which accompanies it, from a dog whose fibrillating ventricles were exposed by operative procedures (Fig. 3).

The next record was taken seventeen minutes later, at 3:05 p. m., and showed the heart beating regularly at a rate of 61.5 beats per minute.

At 3:18 the record (Fig. 4) shows the heart beating at a rate of

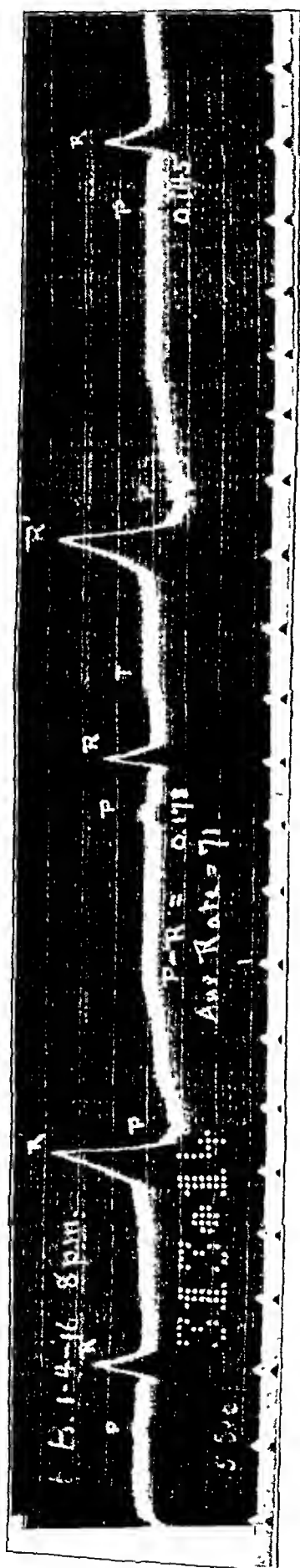


Figure 5-A

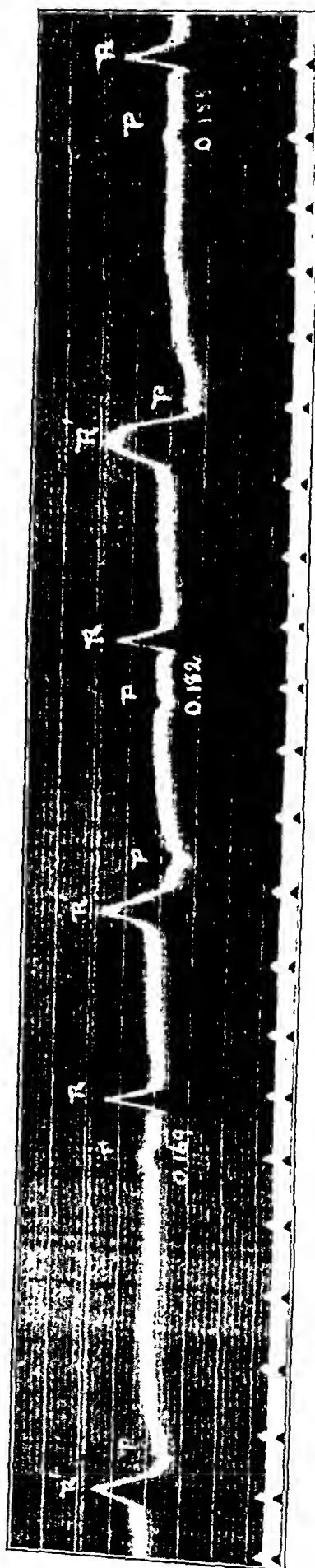


Figure 5-B

Fig. 5.—Obtained five hours after the period of ventricular fibrillation. Various abnormal complexes are seen.

57 beats per minute. The second lead is shown, and it is quite similar in form to that seen in the record obtained on the day of admission. Several unusual complexes occur, however, one of which is shown, a tall broad-based complex occurring prematurely. The P wave is inconspicuous and perhaps diphasic. Records obtained every few minutes after this one showed very little change. That obtained at 4 p. m. (Fig. 4) shows the heart beating regularly 53.6 beats per minute. The P waves have become well defined and no abnormal complexes appear. There is a distinct delay in the A-V conduction time. At 8 p. m. the



Fig. 6.—Three usual leads, twenty hours after the period of ventricular fibrillation, immediately before strophanthin was administered.

heart was beating irregularly (Fig. 5). Ectopic, premature ventricular contractions, yielding constantly varying complexes, were occurring after every normal beat. There was no delay in the A-V conduction time. The auricles were also beating irregularly, and at times the complexes yielded by premature contractions are unusual in form and vary from beat to beat.

No records were obtained at the time of the third period of unconsciousness and convulsive seizure.

At 9:45 a. m., on January 5, records were obtained immediately

Fig. 7.—Record obtained immediately after the intravenous injection of strophanthin.

before the intravenous injection of 1 mg. of strophanthin (Fig. 6). The three leads are shown, and indicate that the cardiac activity was much as it had been the night before, abnormal complexes following all normal complexes. The form of the abnormal complexes show further changes, however.

The record obtained at 10 a. m., ten minutes after the strophanthin was given, shows many abnormal ventricular complexes following one another in rather rapid and irregular succession (Fig. 7). Only one sequential beat appears. This record indicates that numerous points in the ventricles were generating stimuli which spread over various paths through the ventricles. This record is of interest as regards the relation of the cardiac activity which it represents and fibrillation, as has been shown in experimental ventricular fibrillation, a point that will be referred to later.

The last record was obtained at 11:40 a. m., about nine hours before death, when the auricles were beating at a rate of 123 beats per minute (Fig. 8). Partial heart block and ectopic premature ventricular contractions occurred. The sequential beats yield complexes, however, quite similar to those obtained when the patient first entered the hospital, and, as far as this evidence goes, the occurrence of ventricular fibrillation produced no change which caused alterations in the sequential ventricular complexes.

Necropsy 587.—For the notes of the necropsy we are indebted to Dr. Opie.

Anatomic Diagnosis.—Bilateral carcinoma of the ovaries; chronic fibrous endocarditis of the mitral and aortic valves; hypertrophy of the left auricle and of the right auricle and ventricle; chronic passive congestion of the liver and spleen; edema of the lungs; bronchopneumonia; peritoneal effusion; chronic diffuse nephritis, with granular kidneys, of normal size; old pleural adhesions; arterial sclerosis; healed tuberculosis of the bronchial lymph nodes.

The heart weighs 290 gm. On the surface is a scant amount of fat which has a translucent, edematous appearance. The heart muscle is firm and red-brown in color. The thickness of the left ventricle is 16 mm. The left auricle has thickened walls measuring 2 mm. The endocardium has a gray, thickened appearance. The right ventricle is thickened, measuring 4 mm. The right auricle is also somewhat thickened. The mitral orifice measures 8 cm. The valve is thickened and the segments are fused together so that the valvular orifice is contracted. The valve segments are firm. The free edge is rounded and retracted. Just above the free edge there are several projecting vegetations. The chordae tendinae are thickened and shortened. The aortic orifice measures 6.7 cm. The semilunar folds are intact, but the free edges are slightly thickened and rounded, particularly in the neighborhood of the corpora arantii, from one of which there is a small projecting vegetation. The tricuspid orifice measures 11 cm., while the pulmonary orifice measures 7.7 cm. These valves are normal. The main branches of the coronary arteries are patent. An occasional elevated, yellowish area occurs in their lumen. The thoracic and abdominal aorta is thickly studded with elevated plaques, usually 0.5 to 1 cm. across, of yellowish color.

Microscopic examination of the heart muscle of both auricles and ventricles fails to reveal any distinctive lesion. The muscle fibers have a loose appearance as though separated by fluid, and there is moderate fragmentation. There is a slight general small round cell infiltration.

The necropsy throws no light on the cause of the ventricular fibrillation. It has been shown by Lewis⁶ that obstruction to the blood flow through the coronary arteries in animals may result in ventricular fibrillation. The moderate grade of sclerosis of the coronaries in the case reported indicates, however, that the coronary blood supply was probably not materially interfered with, although the presence of vegetations on the mitral and aortic valves permits of the possibility of a coronary embolus which escaped detection at necropsy. The definite signs of cardiac insufficiency suggest the possibility of improper blood supply of the heart muscle as one of the results of this insufficiency. This may have been a factor in the production of the transient fibrillation of the ventricles.

Levy⁷ has described an effect of light chloroform anesthesia which renders the ventricles especially prone to fibrillation. Ventricular fibrillation is then readily produced by the injection of epinephrin. The fibrillation produced by this method is always preceded by a stage of complex ventricular irregularities. Levy believes that fibrillation is a still more advanced and complex grade of these ventricular irregularities. They have been studied by means of electrocardiograms by Levy and Lewis,⁸ who have shown that the ventricular irregularities preceding fibrillation consist in ectopic ventricular contractions arising from numerous foci. They consider this type of derangement of the heart beat as a transitional stage towards ventricular fibrillation, and have observed it also after recovery from fibrillation. Levy has called this condition, when ectopic beats arise from multiple foci in the ventricles, a state of potential fibrillation. The electrocardiogram shown in Figure 8, obtained immediately after the injection of strophanthin, is similar to those obtained by Levy and Lewis during this period of so-called potential fibrillation.

Much light has been thrown on the functional derangements of the heart which underlie fibrillation by the work of Mines⁹ and of Garrey.¹⁰ The former has studied the effect of successive induction shocks on the frog's heart, and found that under certain conditions which allow the muscle to respond to a rapid series of shocks, the refractory period of the muscle becomes shortened and the rate of propagation of the wave

6. Lewis: *Mechanism of the Heart Beat*, London, 1911, p. 160.

7. Levy: *The Exciting Causes of Ventricular Fibrillation in Animals Under Chloroform Anesthesia*, *Heart*, 1912-1913, **4**, 319. *The Genesis of Ventricular Extrasystoles Under Chloroform: with Special Reference to Consecutive Ventricular Fibrillation*, *Heart*, 1913-1914, **5**, 299.

8. Levy and Lewis: *Heart Irregularities Resulting from the Inhalation of Low Percentages of Chloroform Vapor, and Their Relationship to Ventricular Fibrillation*, *Heart*, 1911-1912, **3**, 99.

9. Mines: *On Dynamic Equilibrium in the Heart*, *Jour. Physiol.*, 1913, **46**, 349.

10. Garrey: *The Nature of Fibrillary Contraction of the Heart; Its Relation to Tissue Mass and Form*, *Am. Jour. Physiol.*, 1914, **33**, 397.

of excitation becomes slowed. Mines advanced an hypothesis explaining fibrillation based on these observations. He believed that when these changes occur a portion of the ventricular musculature goes very briefly into contraction, and the refractory period of this particular portion passes off before the impulse which travels slowly through the ventricular musculature again reaches it. Then this portion can go again into contraction. He suggests that such a circulating rhythm may constitute the condition known as ventricular fibrillation.

Garrey,¹⁰ whose work was reported before that of Mines appeared, has carried the knowledge of the nature of fibrillation further, and by an ingenious experiment has been able to observe directly the passage of waves of muscular contraction through the heart muscle, which continued uninterruptedly to effect successive portions of the muscle, returning again and again to the same portion. His experiments form an adequate basis for his belief that fibrillary contractions of the heart muscle depend on the establishment within the musculature of multiple regions of block or reduced conductivity. The impulses thus blocked or delayed take abnormal and circuitous paths, and return to the same portion of the muscle after the refractory state has passed off, but while other portions are still refractory. The latter portions are subsequently involved in a similar manner, and the whole tissue mass is thus thrown into a continuous incoordinated contraction, which is not initiated or sustained by new impulses arising from any definite location.

The electrocardiograms of the patient here reported obtained after the attack of fibrillation indicate that there was present in the ventricles functional abnormalities which apparently predispose to fibrillation. The abnormal ventricular complexes, which vary greatly in form, indicate that cardiac impulses were arising in various points in the ventricles, and that these impulses were travelling through the ventricular musculature along abnormal paths. Many of these complexes are remarkably prolonged, especially in their initial phase, indicating that the impulses were passing through the musculature at an abnormally slow rate. These abnormalities are indicated most strikingly in the record obtained just after the intravenous injection of 1 mg. of strophanthin. The fact that the drug apparently brought the heart more definitely into the so-called state of potential fibrillation, seems worthy of emphasis in view of the fact that sudden death, perhaps from ventricular fibrillation has not infrequently occurred after the use of this drug. We have recently had one such experience, and a number of others have been reported to us verbally.

It seems probable that ventricular fibrillation is prone to occur in hearts in which there is a disturbance of the conduction of the impulse of the heart-beat through the ventricles. Such a disturbance would tend to produce the conditions which Mines and Garrey have described

as underlying fibrillation. A disturbance of intraventricular conduction may be detected by means of electrocardiograms, as has been recently pointed out by one of us,¹¹ and when such a disturbance is present it should be taken as a contraindication for the use of such drugs as chloroform, epinephrin and strophanthin, which predispose the heart to ventricular fibrillation. The case of sudden death which we observed after strophanthin yielded electrocardiograms suggesting such a disturbance, but unfortunately at that time we had not come to recognize their significance.

There is no direct indication as to why the heart in the case here reported should have recovered after ventricular fibrillation became established. The ventricles were relatively small, and would, therefore, be more likely to recover than those of a larger heart, as Garrey has shown that there is a definite relation between the size of the muscle mass involved and recovery. It is well known that recovery from ventricular fibrillation is not uncommon in smaller animals, as Gunn¹² has shown for at least one type of fibrillation in the rat. The larger the species or the larger the animal of a species the less likely is recovery from ventricular fibrillation to occur. This case is the first example of cardiac recovery from well established ventricular fibrillation that has been observed in man.

SUMMARY

A case is reported in which the patient showed marked cardiac insufficiency and had three attacks of cardiac syncope. During one of these attacks an electrocardiogram was obtained which is typical of ventricular fibrillation. The patient lived thirty hours after this syncopal attack, and numerous electrocardiograms were obtained during this time. One immediately after the intravenous injection of strophanthin showed a deranged cardiac mechanism similar to that observed experimentally by Levy and Lewis during the so-called state of potential fibrillation. The abnormal forms of ventricular complex which occurred frequently, were such as to indicate that there was a derangement of intraventricular conductivity. This may have been the prime factor in the production of the ventricular fibrillation. The occurrence of ventricular complexes indicative of derangement of intraventricular conductivity should be taken as contraindication for the use of drugs such as chloroform, epinephrin and strophanthin, which predispose the heart to ventricular fibrillation.

The foregoing case is the first example of cardiac recovery from well established ventricular fibrillation that has been observed in man

11. Robinson: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, *THE ARCHIVES INT. MED.*, 1916, **18**, 83.

12. Gunn: Ventricular Fibrillation in the Rat's Heart, *Heart*, 1913-1914, **5**, 1.

LOCALIZED AND INTERLOBAR PNEUMOTHORAX COMPLICATING PULMONARY TUBERCULOSIS*

MAURICE FISHBERG, M.D.

NEW YORK

In our eagerness to discover tuberculous disease in the so-called incipient stage, we are apt to neglect the study of the symptoms and signs of the chronic forms of phthisis, though it is well known that the prognosis is quite favorable in the majority of the latter class of cases, even though they are designated as "advanced." Indeed, while caring for active cases of pulmonary phthisis we often attribute all the usual and unusual symptoms, the acute and subacute exacerbations and complications to one cause—the tubercle bacillus—and we forget that the lesions produced in the lungs by these bacilli are multifarious, and the prognosis in each is to be formulated by a study of the underlying changes noted in the individual patient. It is a matter of fact that in the vast majority of cases we can ascertain the exact pathologic, and often the etiologic, factors responsible for the sudden, or insidious, changes observed during the long and tedious course of the active period of the disease. Some of the complications which influence the prognosis are more or less easily discernible, as is the case with laryngeal, intestinal or peritoneal tuberculosis, pleurisy, spontaneous pneumothorax with complete collapse of the lung, etc.; but there are others which often escape detection, unless carefully watched for, all modern diagnostic aids being applied, and the findings properly interpreted.

Among the latter class of complications are the latent, partial, and interlobar forms of pneumothorax, which are quite frequent in cases of active phthisis, but only rarely recognized. Even when suspected, the localized form of pneumothorax is, in most cases, confused with large pulmonary excavations. Moreover, some are inclined to think that the differentiation between large pulmonary cavities and circumscribed pneumothorax is merely a pedantic diagnostic trick, at most of academic interest. "What difference does it make whether the cavity made out is in the lung or in the pleura? In either case the patient is doomed," said a physician to me recently. But in many cases it does make a great difference as regards the immediate and ultimate outlook. A patient with a localized pneumothorax may recover. In fact, it was this class of cases which gave the first impulse to treat certain phthisical

* Submitted for publication June 20, 1917.

* From the Tuberculosis Pavilion of the Montefiore Home and Hospital for Chronic Diseases.

tions usually show large, moist, consonating râles and gurgles. A large "dry" cavity, especially when extending to the axilla, should not be accepted as such without careful investigation. The breath sounds in pneumothorax are distinctly amphoric or metallic; such exquisite metallic sounds are exceedingly rare in cavities. But it must also be borne in mind that in the former there may be feeble, or entire absence of, breath sounds, which is also true of cavities, especially when the communicating bronchus is plugged by secretions or swollen, or when it is altogether filled with secretions. In cavities we at times perceive metamorphosing breathing, which is never heard in pneumothorax. On the other hand, in some cases of pneumothorax a metallic tinkle is heard; in cavities, very rarely.

Of great diagnostic importance in the differentiation of these two conditions is auscultation of the whispered voice sounds. In cavities bronchophony is the rule and whispered pectoriloquy is frequently absent, while in localized pneumothorax the latter is commonly present and is strikingly pronounced, clear and articulate, usually perceived as if spoken directly into the stethoscope, a phenomenon exceedingly rare in pulmonary excavation, in which only the spoken voice is transmitted. The whispered echo is also more frequently heard in pneumothorax. Moreover, in localized pneumothorax, especially in the interlobar variety, whispered pectoriloquy is distinctly, or exclusively, heard high up in the axilla, which is very rare in cases with excavations. This is a diagnostic point which is very reliable, and it is rather curious that it has not heretofore been emphasized, or even mentioned. A sharp echo, audible when the patient coughs, may be heard in both conditions, but its ringing quality is more pronounced, as a rule, in pneumothorax.

Percussion may give some criteria for diagnosis. Over cavities the note elicited is dull, and only in very emaciated patients, with excavations located superficially, do we find tympany over a circumscribed area. In pneumothorax tympany is more frequently elicited, at least a tympanitic overnote, and in the interlobar variety it is very clear high up in the arm pit. Cracked-pot resonance may be elicited in both conditions, though more frequently in cavities; the same is true of Wint-rich's sign. The coin test is of value, when positive; it is exceedingly rare in cases with cavities, while over localized pneumothorax it is at times found. In some it is found only in certain positions; it may be present on one day and absent on another.

On inspection of the chest we may get some hints as to the intrathoracic lesion. Retraction of the chest wall is characteristic of large cavities, while bulging may be found, though rarely, in cases of localized pneumothorax. Recalling that in nearly all chronic cases there are pleural adhesions of greater or lesser density, otherwise the pneumo-

thorax would be complete, we have a reason why retraction and flattening of the chest wall over the site of the air pouch is at times found with a localized pneumothorax, and the intercostal spaces are not always wider than their mates on the opposite side. But when found, separation of the intercostal spaces is pathognomonic of a localized pneumothorax, because it is only rarely seen in cavitary cases. This is usually best observed on the roentgenogram. It is noteworthy that in Case 7 reported here the ribs are widely separated, though the necropsy showed a cavity (Fig. 7).

The location of the mediastinal organs gives no reliable clue as to the true lesion. They are almost invariably displaced toward the side affected with a large cavity. In many cases, when the heart has thus been displaced, a small localized pneumothorax subsequently formed in the same side, may not be effective in pushing it back to the opposite side. When the pneumothorax is more extensive and the adhesions not old and dense, the heart may be displaced. But in many cases, as we have seen, the heart remains in its normal place, or is found displaced toward the affected side, just as in cases with excavations. The reason has just been indicated — old adhesions hold it fast in the place it was before the rupture of the pleura occurred.

The roentgenographic findings are invaluable in most doubtful cases. A bright, circumscribed area, lacking in lung markings, when not surrounded by a thick, dark shadow, is pathognomonic of a localized pneumothorax. But at times even this is deceptive. The air pouch may be located anteriorly, while posteriorly is adherent lung tissue which screens it, and no bright area appears on the roentgenogram, as I have seen in some cases. On the other hand, the walls of the pulmonary cavity may not cast a shadow on the roentgenogram, and as a result we may find on the plate a picture clearly showing a pneumothorax, while the real lesion is a large pulmonary cavity, as is well illustrated in Cases 6 and 7 here reported. Such anomalous findings at necropsy have been reported by many clinicians and roentgenographers. It seems to me that in such doubtful cases fluoroscopy is of more value than roentgenography. In localized pneumothorax we often see the mediastinum rhythmically moving during the respiratory act; during inspiration it is moved toward the affected side. This is best seen in artificial pneumothorax, after the first one or two fillings, when there is but a small air pouch in the pleura. In the spontaneous variety, when the adhesions are not dense enough to hold the mediastinum very fast, we may observe the same phenomenon, and this is never seen in cases of large cavities. In most cases it is, however, easy to differentiate on the roentgenogram between cavities and localized pneumothorax. In extensive disease, pulmonary cavities are usually

multiple; they contain not only air, but also secretions which are not constant in quantity, changing intermittently, and bridges made up of connective tissue and blood vessels. No clear, bright area lacking in lung markings is, as a rule, produced on the roentgenogram; their margins are more opaque and the pulmonary tissue around them is denser than in localized pneumothorax. Bearing these points in mind, we may differentiate the two conditions in most doubtful cases. In some, as we have shown, this is impossible.

57 East Ninety-Third Street

STUDIES ON BLOOD SUGAR*

LOUIS HAMMAN, M.D., AND I. I. HIRSCHMAN, M.D.
BALTIMORE

I

ALIMENTARY HYPERGLYCEMIA AND GLYCOSURIA AS A TEST OF SUGAR TOLERANCE

Jacobsen,¹ in 1913, published an interesting study of the effects of different food stuffs on the blood sugar. The food was given from two to three hours after a light breakfast and the blood sugar estimated by Bang's micromethod at short intervals thereafter. He found that protein and fat have no influence on the blood sugar, but that carbohydrate produces a rapid and often a marked hyperglycemia. Following the administration of 100 gm. of glucose, the blood sugar, according to Jacobsen, rises rapidly, often going to 0.16 per cent. and higher, and then falls more gradually to the original level or in some instances even to a lower level, the whole reaction lasting from one to three hours.

A perusal of Jacobsen's results suggested the use of a similar method to study carbohydrate tolerance. Perhaps the character of the curve might be altered in different diseases, and the test therefore yield important clinical data. In spite of the complex mechanism of carbohydrate metabolism, and our scant knowledge of the part played by the different factors concerned in the storage, mobilization and utilization of sugar, the simple estimation of a patient's ability to dispose promptly of a certain amount of glucose taken at one time into the stomach, or as usually named, his glucose tolerance, has definite clinical value. The method generally employed for this purpose is to feed patients glucose in increasing amounts until sugar appears in the urine. There are difficulties and inconveniences in the way of carrying on such an investigation. It is rarely possible to hit on the proper amount of glucose at the first dose, and therefore the test must be repeated a number of times. Solutions of glucose above 100 gm. make a nauseous draught for most patients. Not infrequently they vomit the mixture, and the test must be abandoned. Besides these difficulties, there are also sources of error in the method because

* Submitted for publication Dec. 29, 1916.

* From the Medical Clinic of the Johns Hopkins Hospital.

1. Jacobsen: *Biochem. Ztschr.*, 1913, **56**, 471.

no account is taken of the renal threshold for glucose. Sometimes otherwise normal persons have a low renal threshold and sugar appears in the urine although the blood sugar is only a little raised; more commonly still, renal permeability is decreased and little sugar or none comes out in the urine although the blood sugar mounts to a high level. Under such circumstances one would conclude erroneously, in the first instance, that the patient had a low sugar tolerance; in the second instance, a high sugar tolerance. It would be a decided advantage could we give a single and constant dose of glucose and from a study of the patient's reaction satisfactorily determine the sugar tolerance. We believe that the method we have employed furnishes us this information in an altogether satisfactory way, and that it adds, besides, an insight into the carbohydrate economy that the rougher tolerance test does not give.

METHOD

The patient to be tested receives 100 gm. of glucose in a lemonade in the morning after the night fast. We have found it advisable to prepare the lemonade by dissolving the glucose in warm water, adding the juice of several lemons, or of two lemons and an orange, making the mixture up to 300 c.c., and cooling by packing in ice, or by adding ice before serving. Such a mixture is not disagreeable to take, and rarely causes nausea. If larger quantities of water are used patients often complain of the bulk, and sometimes of nausea after drinking it. The blood sugar is determined before the glucose is given, and thereafter at frequent intervals. Specimens of urine are collected immediately before or immediately after each blood specimen is taken; or, if the patient is unable to void so frequently, as often as they can be obtained. The urine is carefully examined for sugar, and if sufficient be present the quantity is determined separately in each specimen. The blood is obtained by puncture of an arm vein at the bend of the elbow, a little over 2 c.c. of blood being withdrawn at each puncture. It may seem a formidable procedure to undertake so many venipunctures at short intervals, but in fact it is neither difficult for the operator nor disagreeable to the patient. If a vein has once been fairly entered the needle may thereafter be passed in through the same puncture and the patient scarcely be aware of the operation. The only important warning is to avoid making suction until the needle is fairly in the vein, and to desist before the needle is withdrawn. A small hematoma may so obscure the location of the vein that another site must be selected for the next puncture. In fat subjects this is often a disadvantage. We are assured by patients who have had experience with both methods that repeated pricking of the ear or finger tip is more dis-

agreeable than an equal number of venipunctures skilfully performed. In these studies we have made more frequent blood sugar determinations than are really necessary. We believe that four determinations, one before administering the glucose, and others a half hour, one hour and two hours after, will give all needed information.

We have used the Lewis-Benedict² blood sugar method following the technic originally described. Numerous control estimations on glucose solutions of known strength have convinced us of the remarkable accuracy of the method. Heating the mixture in a test tube over a free flame is tedious and time consuming, but we have been unable to get accurate results in other ways, and we have tried heating over a steam bath and in the autoclave at different pressures. In examining the urine Benedict's³ qualitative and quantitative methods were employed.

REACTIONS IN NORMAL PERSONS

Jacobsen's studies on alimentary hyperglycemia following the administration of 100 gm. of glucose were made on fourteen so-called normal persons. The blood sugar rose to a maximal concentration of from 0.12 per cent. to 0.23 per cent. The rise occurred rapidly, the highest point being reached in from fifteen minutes to one hour, the fall more gradually, the reaction occupying from forty-five minutes to three and one-half hours. Most of the persons tested by Jacobsen had a single urine examination, but some had two, and a few three. The six whose blood sugar did not rise above 0.16 per cent. had no sugar in the urine; the eight whose blood sugar went above 0.17 per cent. did have glycosuria.

We are unwilling to allow that Jacobsen's figures be accepted as the standard for normals. It is generally conceded that normal persons do not have sugar in the urine after the ingestion of 100 gm. of glucose, even when the glucose is taken into a fasting stomach. Undoubtedly most of Jacobsen's subjects had a somewhat lowered carbohydrate tolerance. Our results, as well as those obtained by Hopkins, support this contention.

Hopkins⁴ has studied the effects of 100 gm. of glucose on eight normal persons. The blood sugar rose to a maximal concentration of from 0.11 per cent. to 0.156 per cent., the highest point being reached in from thirty minutes to two hours. In the six instances followed to the end of the reaction, the reaction occupied from one and a half to three and a half hours. No urine examinations are reported.

2. Lewis and Benedict: *Jour. Biol. Chem.*, 1915, **20**, 61.

3. Benedict: *Jour. Am. Med. Assn.*, 1911, **57**, 1193.

4. Hopkins: *Am. Jour. Med. Sc.*, 1915, **102**, 254.

In Chart 1* is given the results of our study of six normal persons. After 100 gm. of glucose the blood sugar rose to a maximal concentration of from 0.1 per cent. to 0.13 per cent. The rise to 0.148 per cent. was after 200 gm. of glucose. The high point was reached in from twenty minutes to one and a half hours. The whole reaction occupied from one to two hours. Although the blood sugar of none of the six rose to 0.15 per cent. still two showed glycosuria. In one of these the blood sugar went to 0.124 per cent., in the other to 0.138 per cent. (Charts 2 and 17). We have established, as will subsequently appear, that the normal renal threshold for glucose is between 0.17 per cent. and 0.18 per cent. of blood concentration. Therefore, these two patients have an unusually low renal threshold; perhaps one might speak of it as a potential renal diabetes.

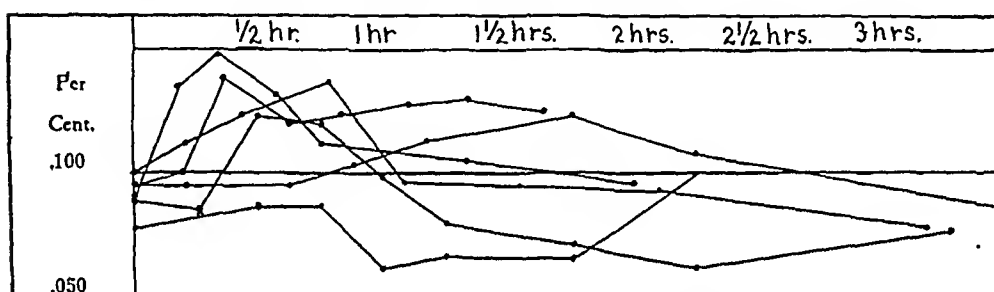


Chart 1.—A composite chart illustrating the blood sugar curve in five healthy persons after the ingestion of 100 gm. of glucose, and in one after 200 gm.

SUMMARY

In normal persons, after the ingestion of 100 gm. of glucose the blood sugar rises promptly to a level not exceeding 0.15 per cent.; the high point is reached usually in about thirty minutes; from the high point the blood sugar may fall off as quickly as it arose, but as a rule the fall is more gradual; the whole reaction lasts from one to two hours, occasionally longer. A certain number of otherwise normal persons have a low renal threshold for glucose so that sugar appears in the urine, although the blood sugar remains below 0.14 per cent.

*In the charts the heavy line represents the blood sugar curve, each dot on the curve denoting a blood sugar estimation. The base line is drawn at 0.1 per cent. since the blood sugar level of fasting normal persons never exceeds this amount. In the adrenalin charts the systolic and diastolic blood pressure readings are marked by fainter solid lines. The scale to the left of the chart serves for both the blood sugar and the blood pressure, that is, 0.150, for instance, indicates 0.150 per cent. of blood sugar, and 150 mm. Hg of pressure. At the bottom of the chart the diuresis and the glycosuria are portrayed; the diuresis by the solid line and the glycosuria by the shaded area. Each dot on the line shows the time at which a specimen of urine was collected. Since the intervals between specimens are irregular the diuresis and the glycosuria are expressed not as absolute figures, but as the rate of flow per hour. The scale to the right of the chart records the diuresis in cubic centimeters, the glycosuria in grams.

CASE 1.—I. H., W. M. S., healthy physician, aged 27, was given the glucose tolerance test, Nov. 29, and the epinephrin test, Nov. 17, 1915. The protocol of the first test is given in Table 1; the data of the second are presented in Chart 17.

TABLE 1.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 1*

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:25	0.096		
8:40	Glucose, 150 gm. in 450 c.c. water		
8:51	0.10	90	0
9:01	0.138	60	0
9:17	0.120	94	Trace
9:30	0.128	230	Trace
9:46	0.128	770	Trace
10:00	0.130	923	0
10:18	0.126	868	

* From 8^h a. m. to 9:30 a. m. the patient drank 1,300 c.c. water.

CASE 2.—H. C., W. M. S., healthy medical student, aged 23, was given the epinephrin test Nov. 17, the glucose tolerance test, Dec. 6, and the atropin-epinephrin test, Dec. 29, 1915. The protocols of the first two tests are given in Tables 2 and 3, respectively; the data of the last test are presented in Chart 18.

TABLE 2.—PROTOCOL OF EPINEPHRIN TEST IN CASE 2*

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:00	Glucose, 50 gm. in 400 c.c. water		
8:45	0.072		
8:50	Epinephrin, 1 mg.		
9:05	0.096		
9:20	0.138	?	0
9:30	0.166	450	1.8
9:40	0.174	444	2.4
10:00	0.154	600	3.0
10:15	0.132	624	2.5
10:30	0.12		
10:40	0.092	320	0.4
11:00	0.068		
11:30	245	

* From 8:50 to 11 the patient drank 1,700 c.c. water.

TABLE 3.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 2

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. per Hour
8:38	0.091		
8:40	Glucose, 200 gm. in 500 c.c. water		
8:50	0.135		
9:00	0.148		
9:10	0.132		
9:25	0.112	143	0
10:00	0.105		
10:40	0.096	175	0

CASE 3.—M. McN., W. M. S., healthy medical student, aged 24, was given the glucose tolerance test, Jan. 14, and the epinephrin test, Feb. 21, 1916. The protocols of these tests are given in Tables 4 and 5, respectively.

TABLE 4.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 3

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:25	0.096		
8:30	Glucose, 100 gm. in 300 c.c. water		
8:42	0.095	44	0
9:07	0.095	374	0
9:23	0.104	572	0
9:40	0.114	60	0
10:15	0.124	157	0
10:45	0.108	364	0
12:00	0.086	251	0

TABLE 5.—PROTOCOL OF EPINEPHRIN TEST IN CASE 3

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:48	0.088		
8:50	Glucose, 50 gm. in 200 c.c. water		
9:00	Epinephrin, 1 mg.		
9:00	0.115	70	0
9:10	0.126		
9:25	0.172		
9:35	0.255	155	0.39
9:53	824	5.06
10:10	0.284	645	7.9
10:45	0.182	116	1.7
11:37	0.085	80	0.98

CASE 4.—H. G., W. M. S., healthy medical student, aged 24, was given the glucose tolerance test, Jan. 30, 1916. The protocol of this test is given in Table 6.

TABLE 6.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 4

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:47	0.101		
9:00	Glucose, 100 gm. in 300 c.c. water		
9:10	0.112		
9:24	0.124		
9:45	0.137		
10:03	0.096		
10:30	0.095	91	0
11:04	0.094		
12:10	0.078	98	0

CASE 5.—J. H., W. M. S., healthy medical student, aged 24, was given the glucose tolerance test, Feb. 3, 1916. The data of this test are presented in Chart 2.

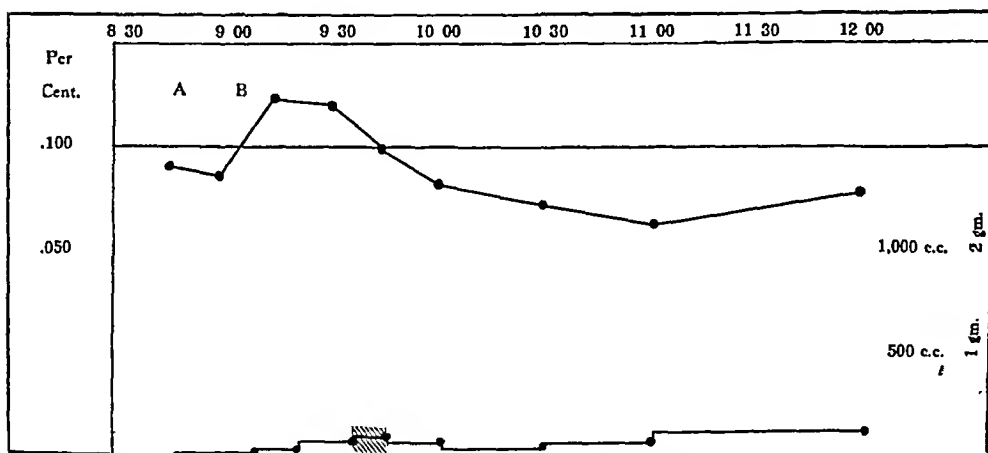


Chart 2 (Case 5).—Normal person. A normal reaction, except that the patient shows a remarkably low renal threshold. The rise is quick, the high point being reached thirty minutes after the ingestion of 100 gm. of glucose. There is no plateau, and the fall is rapid, the whole reaction being over in one hour. Although the blood sugar rises only to 0.124 per cent., as a small amount of sugar appears in the urine. The renal threshold, therefore, is in the neighborhood of 0.12 per cent. There is no special diuresis. At flow patient voided. A, glucose, 100 gm. in 300 c.c. of water; B, water, cubic

CASE 6.—L. G., W. M. S., healthy medical student, aged 23, was given the glucose tolerance test, Feb. 10, 1916. The protocol of this test is given in Table 7.

TABLE 7.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 6			
Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30	0.079		
8:45	Glucose, 100 gm. in 300 c.c. water		
9:00	0.084	98	0
9:15	0.086	93	0
9:30	0.087	100	0
9:46	0.061	405	0
10:00	0.067	385	0
10:30	0.066	464	0
11:00	0.100	104	0

REACTIONS IN DIABETES

Jacobsen reports the effects of 50 gm. of white bread on the blood sugar of five diabetics. Three of the cases were sugar-free when the test was begun; the other two had respectively 0.6 per cent. and 0.36 per cent. of sugar in the urine. Following the administration of 50 gm. of bread, the equivalent of 27 gm. of glucose, the blood sugar rose rapidly, but somewhat slower than in normals, the high point being reached in from one to one and a half hours; this high point was maintained for from thirty minutes to an hour, giving the curve a rounded, instead of a sharp summit; the fall was then gradual, the whole reaction occupying from two to over three hours. In two of the patients, sugar free at the start, the blood sugar did not reach 0.15 per cent., and still appreciable amounts of sugar appeared in the urine. Jacobsen comments on this disproportion, stating that diabetics excrete more sugar at a given blood sugar level than do normals. We have found that in diabetes the renal threshold is often abnormally low and this low threshold is the cause of the difference Jacobsen has noted.

Hopkins has studied the hyperglycemia following the administration of 100 gm. of glucose in nine diabetics. All of these patients had a high blood sugar and glycosuria when the test was given. Hopkins comments on the pronounced hyperglycemia that followed, and the prolongation of the reaction as compared with normals.

We have studied twelve reactions on nine diabetics, administering from 10 to 100 gm. of glucose, according to the severity of the disease. The severity of the disease was judged by the ease with which the patients were rendered sugar free by fasting and their ability subsequently to utilize carbohydrate without the appearance of glycosuria. The cases are thus roughly divided into mild, moderately severe and severe diabetes. Three of the four patients classed as mild diabetics, received 100 gm. of glucose, the other 85 gm. The general clinical

features of the four cases, 7, 8, 9, and 10, and the results of the test are as follows:

CASE 7 (Dispensary No. F-51051).—Diagnosis: diabetes mellitus. B. C., W. M. M., aged 40, gave a history of onset of illness occurring in November, 1915, with polyuria and polydipsia. The patient lost 12 pounds in weight. Examination on Feb. 8, 1916, was quite negative, except for glycosuria. The patient became sugar-free on carbohydrate restriction. The glucose tolerance test was made March 3, 1916. The data of this test are presented in Chart 3.

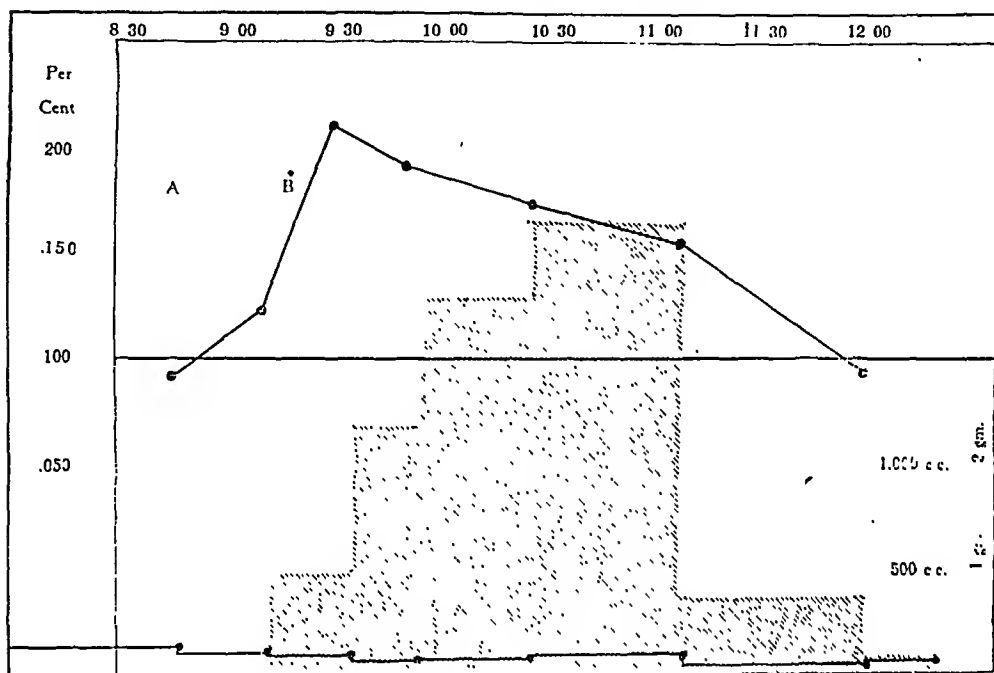


Chart 3 (Case 7).—A characteristic chart from a mild diabetic. The blood sugar rise is rapid, and quite high, the high point being reached three quarters of an hour after taking the glucose. There is no well marked plateau, but the fall is slow and gradual, the whole reaction lasting three and one-quarter hours. On the rise the renal threshold is somewhere between 0.124 per cent. and 0.21 per cent. Since a large amount of sugar is put out in this period, the renal threshold probably is in the neighborhood of 0.18 per cent. This chart shows how the threshold falls as sugar is excreted, for on the down-curve some sugar is still put out even after the blood sugar has fallen as low as 0.094 per cent. There is no special diuresis. During the period of the experiment 6.8 gm. of sugar are excreted. At 8 a. m. the patient voided. A, glucose, 100 gm. in 300 c.c. of water; B, water, 150 c.c.

CASE 8 (Hospital No. 35464).—Diagnosis: diabetes mellitus; angina pectoris; slight hypertension. D. R., W. F. W., aged 53, had had mild attacks of angina for eight years. Sugar was discovered in the urine by a physician, but no symptoms of diabetes were found. On admission to the hospital, Nov. 12, 1915, examination showed an obese woman, signs of slight pulmonary emphysema, blood pressure 160 and 110, abundant sugar in the urine, and slight acetonuria. The patient quickly became sugar-free, and no sugar returned, on carbohydrate-free diet of 1,500 calories with 90 gm. of white bread. Blood sugar on admission was 0.206 per cent.; on March 1, 1916, 0.128 per cent. The glucose tolerance test was made March 6, 1916. The protocol of this test is given in Table 8.

TABLE 8.—PROTOCOL OF THE GLUCOSE TOLERANCE TEST IN CASE 8

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:45	0.091	142	0
8:48	Glucose, 100 gm. in 300 c.c. water		0
9:10	0.124	122	1
9:30	0.210	110	2.4
9:50	0.190	83	3.6
10:25	0.174	94	4.3
11:07	0.155	102	0.8
12:00	0.094	52	0.13
12:21	66	

CASE 9.—F. R., W. M. M., aged 46, came for treatment on April 12, 1915, for an acne rosacea of long standing, and a primary syphilitic sore. Routine examination disclosed a postprandial glycosuria, the morning urine never containing sugar. The glucose tolerance test was made March 13, 1916. The data of this test are presented in Chart 4.

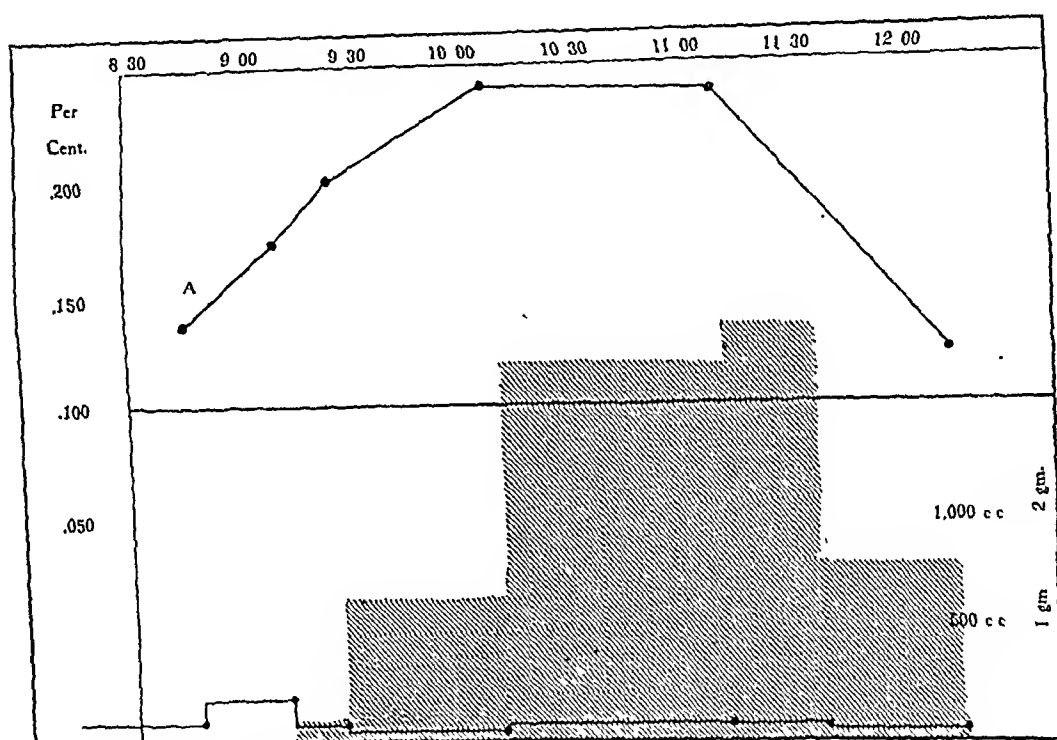


Chart 4 (Case 9).—A characteristic diabetic blood-sugar chart. The rise is a little slow (one and one-half hours); the plateau sustained (one hour); the drop rather abrupt. The threshold on the rise is between 0.171 per cent. and 0.2 per cent. Since a moderate amount of sugar is put out and the rise is abrupt, the renal threshold is in the neighborhood of 0.18 per cent. The threshold on the down-curve is lower than on the up-curve, although it cannot be definitely fixed in the chart. The diuresis is fairly constant, and bears no relation to the glycosuria. During the period of the experiment 7 gm. of sugar are excreted. At 6 a. m. the patient voided, and at 7 a. m., drank a glass of sweetened lemonade. A, glucose, 100 gm. in 300 c.c. of water.

CASE 10 (Hospital No. 35907).—Diagnosis: diabetes mellitus, mild. Discovery was made in the summer of 1915 that the urine of F. V., M. W. M., aged 52, reduced Fehling's solution. The reducing body was decided to be glycuronic acid. The patient came to the hospital in May, 1916, for burning on urination, and sugar was discovered in the urine. No symptoms of diabetes were found. The glucose tolerance test was made, May 26, 1916. The protocol of this test is given in Table 9.

TABLE 9.—PROTOCOL OF THE GLUCOSE TOLERANCE TEST IN CASE 10

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:50	0.103	42	0
9:00	Glucose, 100 gm. in 300 c.c. water		
9:30	0.167	60	0
10:07	0.195	305	0.76
10:45	0.205	426	1.92
11:32	0.182	330	1.65
12:30	0.09	168	Trace

Of the three moderately severe cases, in two, Cases 11 and 12, the test was repeated. The general clinical features of each case, and the results of the test, are as follows:

CASE 11 (Hospital No. 34967).—Diagnosis: diabetes mellitus. C. H. O., M. W. W., aged 25, gave a history of onset of symptoms occurring in October, 1915, with polydipsia, polyuria and loss of weight. On admission to the hospital, Nov. 15, 1915, there was abundant glycosuria and moderate acetonuria. The physical examination showed nothing of importance except the loss of weight. The patient rapidly became sugar-free on fasting. Subsequently a diet containing 80 gm. of carbohydrate caused hyperglycemia (0.136 per cent.) but no glycosuria. The blood sugar on admission was 0.38 per cent.; three days later, 0.08 per cent. The glucose tolerance test was made Nov. 8 and Nov. 12, 1915. The protocols of these tests are given in Tables 10 and 11, respectively.

TABLE 10.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 11, Nov. 8, 1915

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:15	0.072		
9:20	Glucose, 10 gm.		
9:35	0.070		
9:55	0.085		
10:10	0.095		
10:30	?	0
10:50	0.096		
11:15	0.085	?	0

TABLE 11.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 11, Nov. 12, 1915

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
6:30	Carbohydrate— free breakfast		
9:00	0.06		
9:15	Glucose, 50 gm.		
9:45	0.09		
10:00	0.132		0
10:15	0.142	?	
10:30	0.161	93	2.23
10:45	0.184		
11:00	88	2.30
11:30	147	1.13

CASE 12 (Hospital No. 38325).—Diagnosis: diabetes mellitus; arteriosclerosis; hypertension; chronic nephritis (vascular); chronic infectious arthritis; oral sepsis; Dupuytren's contracture; facial paralysis (old). The patient applied to the surgical department for relief from the Dupuytren's contractures. Glycosuria was discovered during the routine examination. On admission to the medical department, Nov. 4, 1915, D. V., W. M. M., aged 60, had moderate glycosuria without acetonuria. The patient was almost sugar-free on slightly restricted diet, and completely sugar-free after a twenty-four-hour fast. There was no glycosuria on a diet containing 75 gm. of carbohydrate. The blood sugar on admission was 0.17 per cent.; on discharge, 0.09 per cent. The blood pressure was 155 and 100. The phenolsulphonephthalein test, made Nov. 13, 1915, was 47 per cent.; Nov. 24, 1915, 47 per cent. The glucose tolerance test

was made Nov. 10, the epinephrin test, Nov. 22, 1915. The data of these tests are presented in Charts 5 and 20, respectively.

CASE 13 (Hospital No. 35469).—Diagnosis: diabetes mellitus. J. J. B., W. M. S., aged 33, gave a history of onset of symptoms occurring October, 1915. Polydipsia and polyuria developed. In January, 1916, digestive disturbances occurred with 25 pounds loss of weight. On admission to the hospital, Feb. 16, 1916, the examination was essentially negative, except for abundant glycosuria and moderate acetonuria. The patient was sugar-free after three days' starvation. On discharge, March 10, 1916, a trace of sugar was found in the urine after 40 gm. of glucose; no sugar was found on a 2,000 calory diet consisting of 140 gm. protein, 40 gm. carbohydrate and 140 gm. fat. The blood sugar on admission was 0.31 per cent.; on discharge, 0.07 per cent. The carbohydrate tolerance test was made February 25 and March 10, 1916, respectively. The protocol of the first test is given in Table 12; the data for the second test are presented in Chart 6.

TABLE 12.—PROTOCOL OF CARBOHYDRATE TOLERANCE TEST
IN CASE 13, FEB. 25, 1916

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:35	0.134	48	0
8:38	Glucose, 40 gm. in 300 c.c. water		
9:00	0.171	139	0
9:30	0.210	97	0.3
9:40	0.288	168	1.68
10:00	0.262	265	2.70
10:48	0.260	277	1.80
11:44	0.264	295	0.97
11:57	120	0.31

The general clinical features of the two severe cases, 14 and 15, and the results of the test are as follows:

CASE 14 (Hospital No. 35506).—Diagnosis: diabetes mellitus; furunculosis; oral sepsis. P. D., W. M. M., aged 39, gave a history of onset of symptoms occurring December, 1915, polydipsia, polyuria and loss of weight. The symptoms were severe for two months, with 60 pounds' loss of weight. The physical examination was negative, except for oral sepsis and furuncle on left forearm. On admission to the hospital, March, 1916, there was abundant sugar, acetone and aceto-acetic acid in the urine. After three days' starvation glycosuria and acetonuria were still present. On discharge, March 18, 1916, the patient was sugar-free on a 1,500 calory diet consisting of 80 gm. protein, 125 gm. fat and 17 gm. carbohydrate. The blood sugar on admission was 0.36 per cent.; on discharge, 0.117 per cent. The carbohydrate tolerance test was made March 17, 1916. The data of this test are presented in Chart 7.

CASE 15 (Hospital No. 35719).—Diagnosis: diabetes mellitus. C. S., W. M. M., aged 24, gave a history of onset of symptoms occurring one year before admission to hospital with weakness, polydipsia and polyuria. The patient was under dietetic treatment most of the year without much improvement. Examination on admission, Feb. 26, 1916, showed a sallow, poorly nourished man, without other important findings. The urine contained abundant sugar, aceto-acetic acid and acetone. The blood sugar was 0.241 per cent.; the alveolar carbon dioxid, 22. After three days' starvation the urine became sugar-free but the acetonuria increased. On a diet of 1,600 calories containing 20 gm. carbohydrate, a small amount of sugar appeared in the urine. The patient finally became sugar free on diet of 1,600 calories containing 9 gm. carbohydrate. On discharge, April 25, 1916, the patient was sugar-free on a diet of 1,500 calories containing 30 to 45 gm. carbohydrate. The blood sugar, March 17, 1916, was 0.146 per cent.; April 4, 1916, 0.119 per cent. The glucose tolerance test was made April 10, 1916. The data of this test are presented in Chart 8.

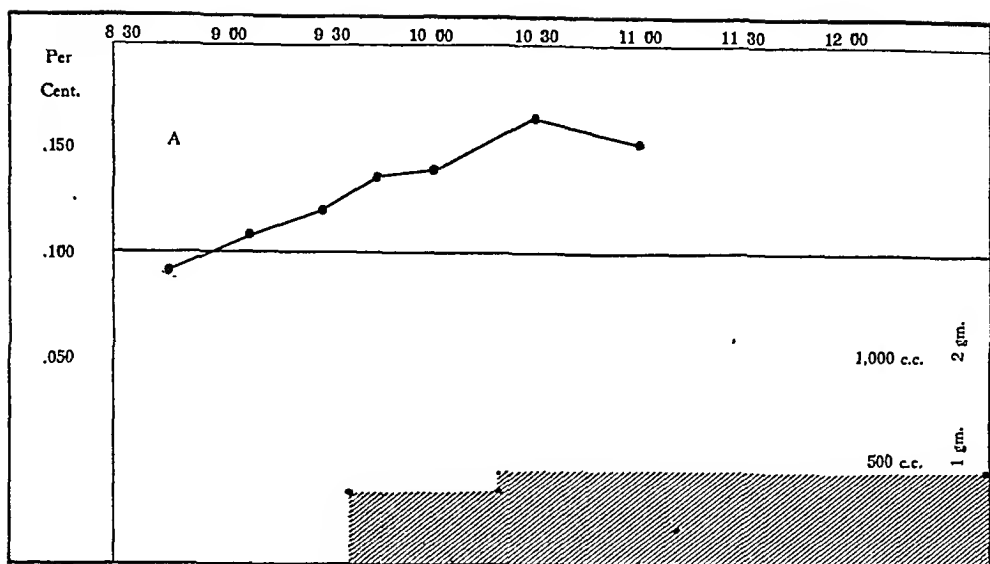


Chart 5 (Case 12).—A typical diabetic chart. The rise is slow, the high point being reached one and three quarters hours after the administration of 50 gm. of glucose. The plateau is sustained, and there is only a little falling off from the high point after two and one-quarter hours. Sugar was excreted before the blood sugar reached 0.15 per cent. The exact threshold cannot be determined. There is no striking diuresis. During the experiment 1.6 gm. of sugar are excreted. At 6:30 a. m. the patient was given a carbohydrate free breakfast. *A*, glucose, 50 gm.

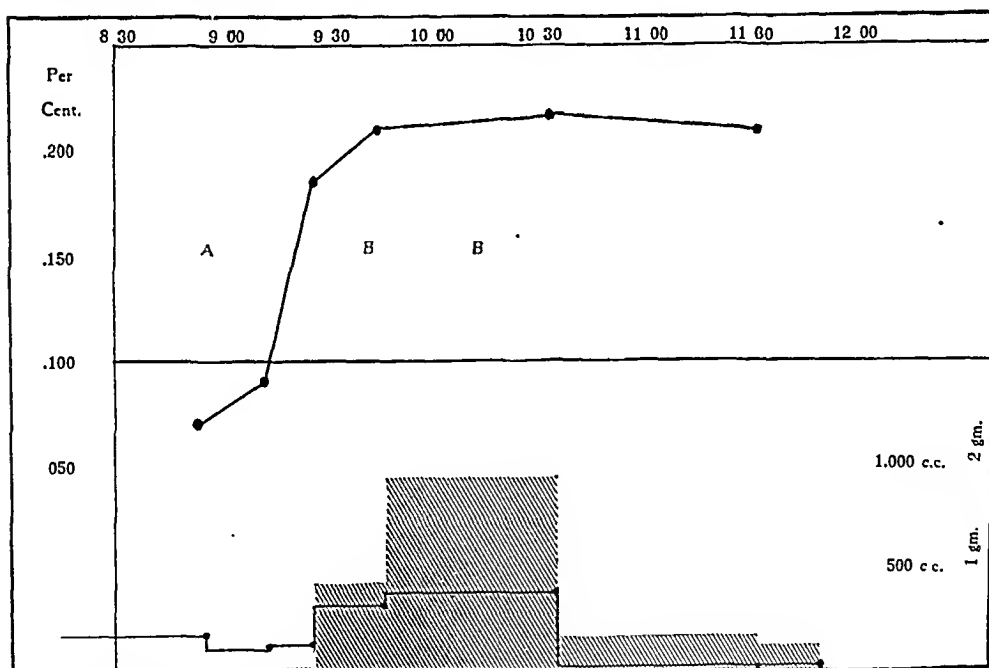


Chart 6 (Case 13).—A characteristic diabetic chart, without lowering of the renal threshold. The rise is very abrupt, the high point being reached forty-five minutes after the administration of the glucose. There is a well sustained plateau, the curve just beginning to fall after two and one-half hours. Judging from the large amount of sugar put out in the specimen passed at 10:35 it is probable that in the preceding period the blood sugar rose higher than is indicated on the chart. Since only a trace of sugar is passed in the urine collected at 9:26 when the blood sugar was 0.185 per cent. the renal threshold is evidently somewhere in the neighborhood of 0.18 per cent. There is a moderate diuresis during the period of marked glycosuria. During the experiment 2.3 gm. of sugar are excreted. At 8:15 a. m. the patient voided. *A*, glucose, 40 gm. in 300 c.c. of water; *B*, water, 100 c.c.

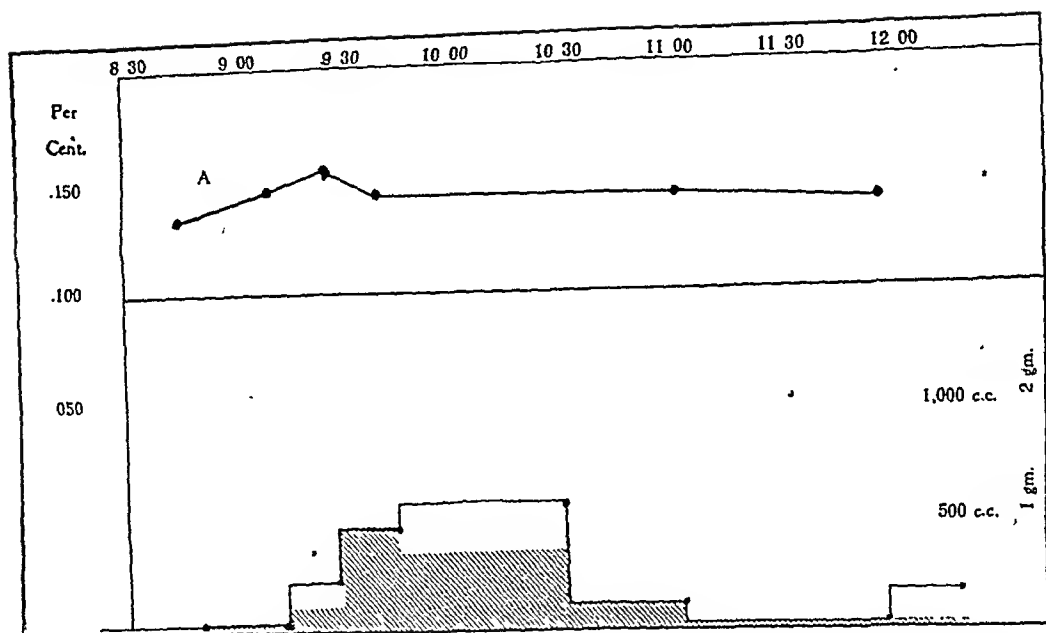


Chart 7 (Case 14).—A characteristic diabetic blood sugar curve, after the administration of 20 gm. of glucose. The blood sugar, high to begin with, rises only a little, the high point being reached in thirty-five minutes. There is then a slight drop; but a point higher than the original level is maintained for over three hours. The threshold is below 0.146 per cent., very likely in the neighborhood of 0.14 per cent. On the down-curve sugar is still excreted after the blood sugar has reached 0.139 per cent. The diuresis during the period of glycosuria is striking, and altogether out of proportion to the amount of sugar excreted. The period of greatest sugar excretion comes immediately after the high point on the blood sugar curve. The total amount of sugar excreted during the experiment is 1.1 gm. At 6:30 a. m. the patient voided. *A*, glucose, 20 gm. in 300 c.c. of water.

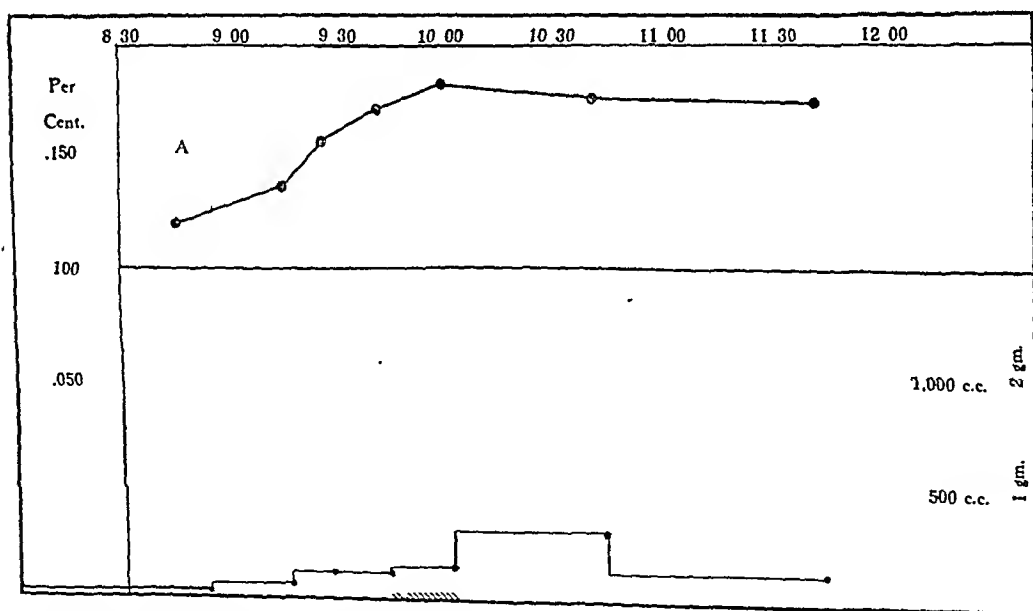


Chart 8 (Case 15).—A characteristic diabetic reaction after 15 gm. of glucose. The blood sugar rises rather slowly, the high point being reached one hour after the ingestion of glucose. Although the reaction extends over three hours, there is at the end of this period just a beginning tendency for the blood sugar to fall off. Only one specimen of urine shows sugar, and this shows only a trace. The threshold, therefore, is accurately fixed in the neighborhood of 0.18 per cent. since the specimen collected when the blood sugar had fallen to 0.178 per cent. no longer contains sugar. There is a rising diuresis, with there is no glycosuria. The kidneys react readily with diuresis, even though there is no glycosuria. At 8 a. m. the patient voided; *A*, glucose, 15 gm. in 300 c.c. of water.

SUMMARY

The reaction of diabetics to the ingestion of glucose was very different from the reaction of normal persons. Our studies do not give strictly comparable data, for only three of the diabetics received 100 gm. of glucose. These three patients, however, having but a mild derangement of carbohydrate metabolism, illustrate strikingly the change in the diabetic reaction as contrasted with the normal. All three had moderate glycosuria during the test, excreting respectively, 6.8 gm., 7 gm. and 3 gm. of sugar. Case 10 had a well marked diuresis during the period of glycosuria, but the large amount of water taken by the patient may account for this. The blood sugar rose more slowly than in the normal, the highest point being reached after forty-five minutes, after one hour and twenty minutes and after one hour and forty-five minutes. It also rose to a much higher level, all three exceeding 0.2 per cent. This high point was maintained for nearly an hour in two instances, for only a short period in the other. The fall of the blood sugar occurred much more slowly than in the normal, the whole reaction occupying from three to four hours.

These general features of the diabetic blood sugar curve are faithfully reproduced by the other patients receiving, on account of the severity of their disease, smaller amounts of glucose. In some of the curves the blood sugar was just beginning to drop three hours after taking the glucose. Apparently the duration of the reaction is a more important index of the severity of the alteration of carbohydrate metabolism than the height of the reaction. In some of the patients a definite diuresis accompanied the glycosuria, and the tendency was particularly noticeable in the severe cases.

REACTIONS IN NEPHRITIS

It has long been known that in nephritis the blood sugar is often unusually high.⁵ However, it is not always high, sometimes it is at the normal level; and why some cases have hyperglycemia and others have not has never been satisfactorily explained. Attempts to bring the hyperglycemia into relation with the blood pressure have not been wholly successful. Hopkins reports a large number of single blood sugar observations on patients with nephritis, and in addition gives the results of an alimentary test on four of the cases. Three of these show a marked hyperglycemia after 100 gm. of glucose, two going above 0.2 per cent. The high point is fairly well sustained,

5. Bang: *Der Blutzucker*, Weisbaden, 1913, p. 128. Rolly and Oppermann: *Biochem. Ztschr.*, 1913, **48**, 268. Bing and Jacobsen: *Deutsch. Arch. f. klin. Med.*, 1914, **114**, 57. Hopkins: Footnote 4. Myers and Bailey: *Jour. Biol. Chem.*, 1916, **24**, 147.

at least the summit of the curve is rounded, and the fall is rather slow, the reaction occupying from three to four hours.

We have made observations on six patients with nephritis. A brief summary of the clinical features of the cases, 16, 17, 18, 19, 20 and 21, and the results of the test follows:

CASE 16 (Hospital No. 35779).—Diagnosis: chronic nephritis; hypertension; arteriosclerosis; myocardial insufficiency; uremia. H. H., B. M. M., aged 49, admitted complaining of shortness of breath. There was an onset of symptoms five months before, with polyuria and nocturia. There was some dyspnea for a year and headaches. On admission to the hospital, March 22, 1916, examination showed a poorly nourished man; Cheyne-Stokes breathing; albuminuric retinitis; cardiac enlargement with systolic murmur and presystolic gallop; thickened vessels; blood pressure 258:180, and slight edema of the ankles. Abundant albumin and casts were found in the urine. The phenolsulphonephthalein test was 30 per cent. and on April 9, 1916, a trace. A progressively downward course terminating in death, May 4, 1916. The anatomic diagnosis revealed primary arteriosclerosis involving particularly the renal arteries, cardiac hypertrophy and dilatation and chronic passive congestion of the viscera. The glucose tolerance test was made March 24, 1916. The data of this test are presented in Chart 9.

CASE 17 (Hospital No. 35716).—Diagnosis: arteriosclerosis; hypertension; chronic nephritis; myocardial insufficiency; chronic bronchitis. L. H., B. F. W., aged 50, gave a history of onset of symptoms occurring over a year before, with dyspnea, cough and wheezing. The symptoms aggravated during the past few months. On admission to the hospital, March 30, 1916, examination showed bronchitis; heart enlarged with loud systolic murmur; diffuse thickening of peripheral vessels; blood pressure 225:130, and edema of legs and over sacrum. The phenolsulphonephthalein test was 37 per cent. Albumin and casts were found in the urine. A renal test meal was given. There was marked nocturnal polyuria with low specific gravity and poor excretion of nitrogen. The glucose tolerance test was given April 3, 1916, the protocol of which is given in Table 13.

TABLE 13.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 17

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:05	0.105		
9:15	Glucose, 100 gm. in 300 c.c. water		
9:30	0.118	19	0
10:00	0.158	54	0
10:35	0.174	91	0
11:10	0.160		0
12:00	0.128	45	0

CASE 18 (Dispensary No. F-10382).—Diagnosis: chronic nephritis; hypertension; dilated aortic arch. M. G., W. M. M., aged 45, gave a history of cough, expectoration and dyspnea for three years. Examination, April 22, 1916, showed an obese man with extreme pyorrhea alveolaris; scattered pulmonary râles; enlarged heart with ringing aortic second sound, manubrial dulness; diffuse arteriosclerosis and blood pressure 240:148. Albumin and casts were found in the urine. The phenolsulphonephthalein test was 33 per cent. The glucose tolerance test was made April 24, 1916. The data of this test are presented in Chart 10.

CASE 19 (Hospital No. 35659).—Diagnosis: chronic diffuse nephritis (?); hypertension and chronic appendicitis. J. S., W. M. M., aged 28, had had

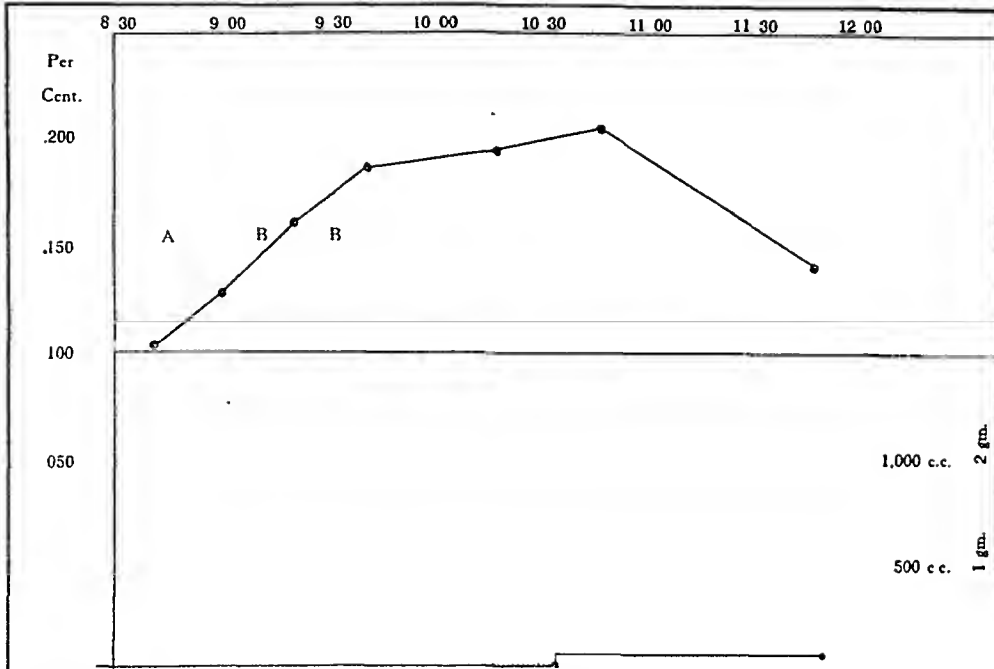


Chart 9 (Case 16).—A diabetic type of chart, with high renal threshold, in a nephritic. The rise is very gradual, the highest point being reached two hours after the administration of glucose. There is a well marked plateau during the second hour. The fall is gradual, and the whole reaction is not over two and one-half hours after taking the glucose. Although the blood sugar goes to 0.205 per cent., only a trace of sugar is excreted in the urine. The threshold is therefore considerably raised. There is no special diuresis. At 8:20 a. m. the patient voided. *A*, glucose, 100 gm. in 300 c.c. of water; *B*, water, 150 c.c.

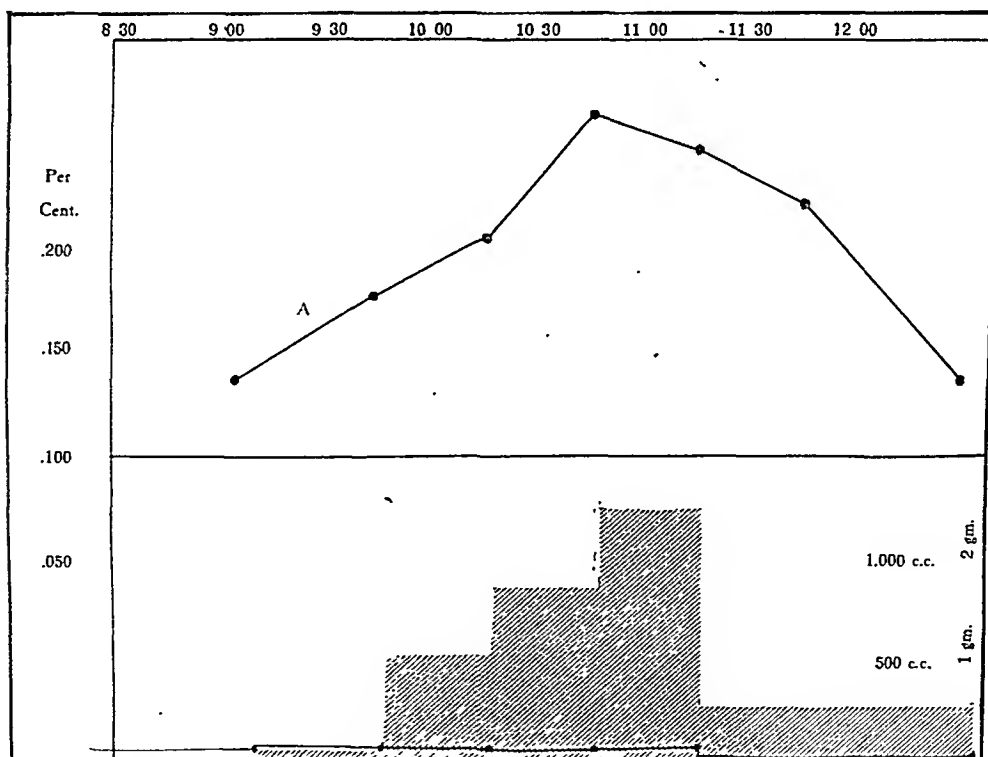


Chart 10 (Case 18).—A typical diabetic type of reaction with normal renal threshold in a patient with hypertension. The blood sugar, high at the outset, rose slowly, reaching the highest point in one hour and twenty minutes. The curve was flattened at the top and the fall was slow, the whole reaction lasting three hours. The renal threshold was in the neighborhood of 0.17 per cent. During the experiment 3.7 gm. of glucose were excreted. At 6:30 a. m. the patient voided; *A*, glucose, 100 gm. in 300 c.c. of water.

for a year and a half attacks of abdominal pain with hematuria. On admission to the hospital, April 13, 1916, examination showed slight general anasarca, blood pressure 188:126 and slight diffuse thickening of arterial walls. There was a trace of albumin in the urine but no casts. The phenolsulphonephthalein test was 78 per cent. A renal test meal was given. There was slight nocturnal polyuria and the specific gravity was fixed at a high level. The glucose tolerance test was made April 7, 1916. The protocol of this test is given in Table 14.

TABLE 14.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 19

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:20	0.106	21	0.08
8:30	Glucose, 100 gm. in 300 c.c. water		
9:10	0.149	54	0.14
9:30	0.161	63	0.13
10:00	0.164	34	0.08
10:30	0.137		
10:58	0.120	43	0.12
11:00	0.111	47	0.12
12:00			

The results of the test were confused by presence of pentose in urine. Some glucose was excreted, as there was slight fermentation in the 9:31 specimen.

CASE 20 (Hospital No. 34529).—Diagnosis: chronic parenchymatous nephritis. J. S., W. M. S., aged 25, gave a history of onset of symptoms occurring shortly before admission, with edema. On admission to the hospital, Aug. 27, 1915, examination showed no noteworthy abnormalities except edema, abundant albumin and casts and a positive guaiac test in the urine. The phenolsulphonephthalein test was 68 per cent. Ambard's coefficient was 0.07. Blood urea nitrogen was 14 mg. per 100 c.c. A nephritic test meal was given; there was normal variation in specific gravity; polyuria and slight nocturnal polyuria were probably associated with elimination of edema. The blood pressure was 120:80. The glucose tolerance test was given April 13, 1916. The protocol of this test is given in Table 15.

TABLE 15.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 20

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:55	0.103	46	0
9:03	Glucose, 100 gm. in 300 c.c. water		
9:30	0.132	29	0
10:00	0.139	52	0
10:30	0.144	50	0
11:00	0.117	24	0
11:30	0.115	28	0
12:30	0.098	19	0

CASE 21 (Hospital No. 35945).—Diagnosis: chronic diffuse nephritis; hypertension; arteriosclerosis. J. B., B. M. S., aged 25, gave a history of onset of symptoms occurring two months before admission with dyspnea on exertion and pain in the abdomen and over the precordium. On admission to the hospital examination showed chronic tonsillitis; cardiac hypertrophy with pre-systolic gallop, and hypertension, 230:180. The vessel walls were diffusely thickened. The urine showed a trace of albumin and many hyalin and finely granular casts. The Wassermann reaction was negative. The phenolsulphonephthalein test was 39 per cent. A nephritic test meal was given, there was nocturnal polyuria and marked fixation of specific gravity at a low level. The first glucose tolerance test was given May 19, the second, June 1, 1916. The protocols of these tests are given in Tables 16 and 17, respectively.

TABLE 16.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 21, MAY 19, 1916

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
6:30	By mistake, break- fast: oatmeal, toast, eggs		
8:45	0.094		
8:48	Glucose, 100 gm. in 300 c.c. water		
8:57	21	0
9:15	0.123	8	0
9:30	0.112	13	0
10:00	0.103	14	0
10:37	0.100	14	0

TABLE 17.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 21, JUNE 1, 1916

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:10	0.092	111	0
8:15	Glucose, 100 gm. in 300 c.c. water		
8:45	0.132	89	0
9:15	0.134	318	0
9:45	0.128	273	0
10:17	0.124	232	0

SUMMARY

The patient (Case 16, Chart 9), with chronic diffuse nephritis and hypertension, bordering on uremia, had a definite "diabetic type" of blood sugar curve, but only a trace of sugar appeared in the urine, although the blood sugar went to 0.2 per cent. The fasting blood sugar was at the upper limit of normal. The renal impermeability explains the absence of glycosuria, in spite of the marked hyperglycemia, but it does not explain the profound disturbance of carbohydrate metabolism portrayed in the blood sugar curve.

The patient (Case 18), with marked hypertension and only moderately impaired renal function, showed a reaction altogether similar to the reaction of a mild diabetic (Chart 10). The fasting blood sugar was high, 0.136 per cent.; the renal threshold was 0.17 per cent.; the blood sugar mounted to 0.264 per cent.; the summit of the curve was rounded; the reaction occupied three hours; a large amount of sugar was excreted. Obviously in this instance renal impermeability played no part in producing hyperglycemia.

Another patient (Case 17) with hypertension and only a moderate impairment of renal function showed a similar though not so marked reaction. The blood sugar curve rose slowly, was rounded at the summit and fell slowly, but the highest point was at 0.174 per cent. and no sugar appeared in the urine.

In contrast with these three reactions is the reaction of the patient (Case 20) with chronic diffuse nephritis without hypertension. The blood sugar curve was a little more prolonged than the normal type, but it did not show the striking diabetic features of the others.

Another patient (Case 19) with chronic diffuse nephritis, without hypertension and with almost normal renal function, showed a some-

what higher and more prolonged blood sugar curve. The urine examinations were equivocal since all of the specimens contained pentose.

These observations influenced us strongly to regard hypertension as an important indicator of disturbed carbohydrate metabolism, and tempted us to seek the common explanation for both in altered epinephrin function. However, a recent observation, temporarily at least, upset this speculation. This observation was made on the patient (Case 21) with chronic diffuse nephritis and hypertension with only moderately impaired renal function. Our first test performed two hours after breakfast yielded a perfectly normal reaction. Hoping that the breakfast might have been accountable for this unexpected result, the test was repeated. Again, a practically normal curve was obtained. In the face of this evidence, we cannot correlate hypertension and alimentary hyperglycemia.

Therefore, in many cases of nephritis there is a profound change in carbohydrate metabolism, the blood sugar curve after the ingestion of glucose resembling the "diabetic curve." When there is marked interference with renal function very small amounts of sugar or none appear in the urine, although the blood sugar may go above 0.2 per cent.

REACTIONS IN DISTURBANCE OF THYROID AND HYPOPHYSIAL FUNCTIONS

Excepting disease of the pancreas, disturbance of thyroid function is the most common cause of altered carbohydrate tolerance. The clinical manifestations of thyroid disease are notoriously variable, and the grouping of the different symptoms occurs in a confusing way. Vagotonic and sympathicotonic symptoms are often hopelessly mixed, and in one patient evidence of overfunction and underfunction may occur side by side. Sugar tolerance shows the same perplexing combinations. However, in a general way in hyperthyroidism it is low, and in hypothyroidism abnormally high, although individual patients display wide latitude in their response. It has been known for a long time that hyperglycemia commonly occurs in exophthalmic goiter, and recently the subject has been studied again in a thorough way by Geyelin.⁶

Since Cushing⁷ has demonstrated the important part played by the hypophysis in carbohydrate economy, disturbance of hypophysial function has come to rank second only to thyroid disease as a fertile source of altered sugar tolerance. In disorders of this gland, as in thyroid disease, hyperfunction is associated with decreased tolerance, hypo-

6. Geyelin: *THE ARCHIVES INT. MED.*, 1915, **16**, 975.

7. Weed, Cushing and Jacobson: *Bull. Johns Hopkins Hosp.*, 1913, **24**, 40.

function with an increase; but similar individual differences occur. Up to the present time, observations of carbohydrate tolerance in thyroid and hypophysial disease consist of urine examinations and of single or at most occasional blood sugar estimations. While these observations have established important facts they give no insight into the underlying metabolic disturbance. Only Hopkins has studied the curve of alimentary hyperglycemia in two cases of hypophysial disease. In both instances there was an abnormally high and prolonged reaction.

We have made observations on six patients with thyroid disease and five with hypophysial disorders. A brief report of the main clinical features of each case and the results of the test follows:

CASE 22 (Hospital No. 38841).—Diagnosis: exophthalmic goiter. E. S., B. M. S., aged 21, had been nervous for three months, and had been growing weak. In October, 1915, exophthalmos was noted. Palpitation and tachycardia developed, with loss of weight. On admission to the hospital, examination showed a moderately emaciated colored man; marked exophthalmos; positive von Graefe's, Stellwag's and Joffroy's signs; struma with systolic thrill and bruit; marked tremor; slight enlargement of heart, and mononucleosis. The blood pressure was 136:64. Loewe's test was positive. The atropin reaction was moderate; the pilocarpin and epinephrin reactions slight. On Dec. 20, 1915, ligation of the superior and inferior thyroid arteries was performed, and on Jan. 8, 1916, left lobectomy was performed. The glucose tolerance test was made Jan. 7, 1916. The protocol of this test is given in Table 18.

TABLE 18.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 22

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30	0.080		
8:33	Glucose, 40 gm. in 300 c.c. water		
8:46	35	0
9:00	0.224		
9:20	0.166		
9:40	0.154	93	1.22
10:00	0.210		
10:30	0.150		
11:00	0.126	85	1.0
12:00	0.120	103	0.43
3:20	90	0

CASE 23 (Hospital No. 38469).—Diagnosis: exophthalmic goiter. F. McD., W. M. M., aged 52, noticed loss of weight in October, 1914, and grew increasingly nervous, with shaking of hands and legs, palpitation and indigestion. Left lobectomy was performed March 1, 1915. Marked improvement followed the operation; the patient gained 30 pounds in weight. In December, 1916, there was a return of nervousness, palpitation, loss of weight and enlargement of thyroid. On admission to the hospital, Jan. 7, 1916, examination showed a neurotic, nervous man; marked tremor; slight von Graefe's sign; definite Möbius' sign; skin moist and warm; fulness of right lobe of thyroid; tachycardia, (94 to 106); mononucleosis, and moderate epinephrin, negative atropin and rather marked pilocarpin reaction. Right lobectomy was performed Jan. 24, 1915, followed by marked general improvement. The first glucose tolerance test was made Jan. 10, 1916, the second, Feb. 16, 1916. The data of these tests are presented in Chart 11.

CASE 24 (Hospital No. 35150).—Diagnosis: exophthalmic goiter. J. O'C., W. M. S., aged 17, gave a history of onset of symptoms occurring two months

before admission, with swelling of neck and increasing prominence of eyes. Subsequently there was palpitation and nervousness. On admission to the hospital, Dec. 20, 1915, examination showed large, elastic struma with bruit and thrill; marked exophthalmos; epiphora; von Graefe's, Dalrymple's and Joffroy's signs; tendency to flushing; slight tremor; slight cardiac enlargement, and tachycardia (88 to 108). The glucose tolerance test was made Dec. 22 and the epinephrin, Dec. 27, 1915. The data of these tests are found in Charts 12 and 21, respectively.

CASE 25 (Hospital No. 39176).—Diagnosis: exophthalmic goiter. L. R., W. F. S., aged 31, gave a history of onset of illness occurring, Feb. 13, 1915, with an attack of grip. During convalescence tremor and trembling came on. The following month there were tachycardia and swelling of the thyroid. Subsequently the patient was very nervous. One attack of stubborn diarrhea occurred. There was hyperhidrosis. Examination on admission to the hospital, Feb. 18, 1916, showed emaciation; marked exophthalmos; moderately enlarged thyroid with slight thrill and bruit; von Graefe's sign, positive; Möbius' sign, slight; Joffroy's sign, negative; marked tremor; tachycardia (75 to 130); blood pressure 128:72; marked reaction to pilocarpin and moderate reaction to atropin and epinephrin. On March 17, 1916, a right lobectomy was performed. The glucose tolerance test was made Feb. 21, 1916. The data of this test are presented in Chart 13.

CASE 26 (Hospital No. 39426).—Diagnosis: exophthalmic goiter. J. R., W. F. M., aged 51, gave a history of onset of symptoms occurring June, 1913, with emotional disturbance, crying, etc., and nervousness. Exophthalmos came on shortly after. Subsequently there was loss of weight, tremor, hot flushes and goiter. A partial thyroidectomy was performed in March, 1914, followed by improvement. During the last four months symptoms returned: headache, flushing, nausea and vomiting, enlargement of goiter, palpitation, nervousness and fright. On admission to the hospital, March 2, 1916, examination showed extreme exophthalmos; marked dermatographia; von Graefe's sign, marked; Joffroy's sign, positive; Möbius' sign, positive; diplopia; struma with systolic thrill and bruit; slight enlargement of heart; moderate diffuse arteriosclerosis; hypertension, 156:72; fine tremor; Loewe's test, positive; marked epinephrin reaction; moderate atropin reaction, and slight pilocarpin reaction. The urine showed a trace of albumin. A left lobectomy was performed April 1, 1916. The glucose tolerance test was made March 31, 1916. The protocol of this test is given in Table 19.

TABLE 19.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 26

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30	0.108		
8:40	Glucose, 100 gm. in 300 c.c. water		
9:00	0.167	356	0
9:30	0.256	280	0
10:00	0.228	202	0
10:32	280	0.2
11:00	0.095	316	0.3
11:30	30	0
11:45	0.067		0
12:10	16	0

CASE 27 (Hospital No. 39846).—Diagnosis: colloid goiter. E. R., W. M. S., aged 16, gave a history of swelling in the neck which began eight years before admission to the hospital. Two years previous mechanical effects began to be noticed; dyspnea; difficulty in bending head; difficulty in swallowing and hoarseness. Physical examination showed nothing of importance other than the huge goiter. Subnormal temperature, slow pulse, dry skin and high sugar tolerance (300 gm. without glycosuria) point to slight hypothyroidism. On May 20, 1916, a right lobectomy was performed. The glucose tolerance test was made April 6, 1916. The protocol of this test is given in Table 20.

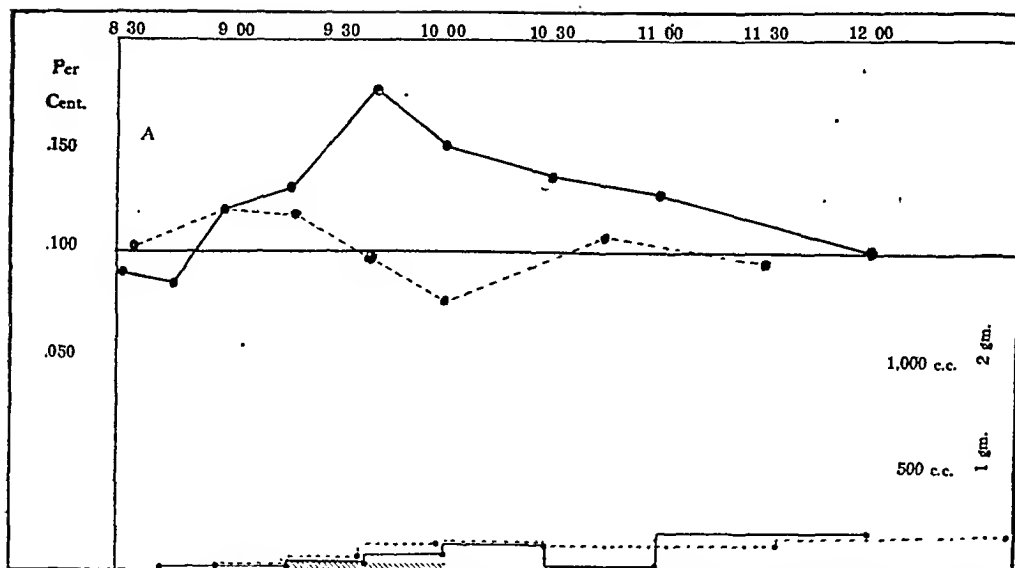


Chart 11 (Case 23).—The curve shows a rather marked and sustained blood sugar reaction after the administration of 100 gm. of glucose, in a patient with hyperthyroidism. The rise is slow, the high point being reached one hour and ten minutes after the administration of the glucose. There is no plateau, but there is a very gradual fall, the original level of blood sugar being reached after three and one-half hours. Sugar is excreted between 0.15 per cent. and 0.176 per cent. Since only a very small amount of sugar is put out, the threshold is probably in the neighborhood of 0.17 per cent. There is nothing striking about the diuresis. The most marked urine output occurred toward the end of the curve. During the experiment, about 0.04 gm. of sugar is excreted. The curve represented by the dotted line shows the patient's reaction to the same test one month after operation. It is a normal curve. A, glucose, 100 gm. in 300 c.c. of water.

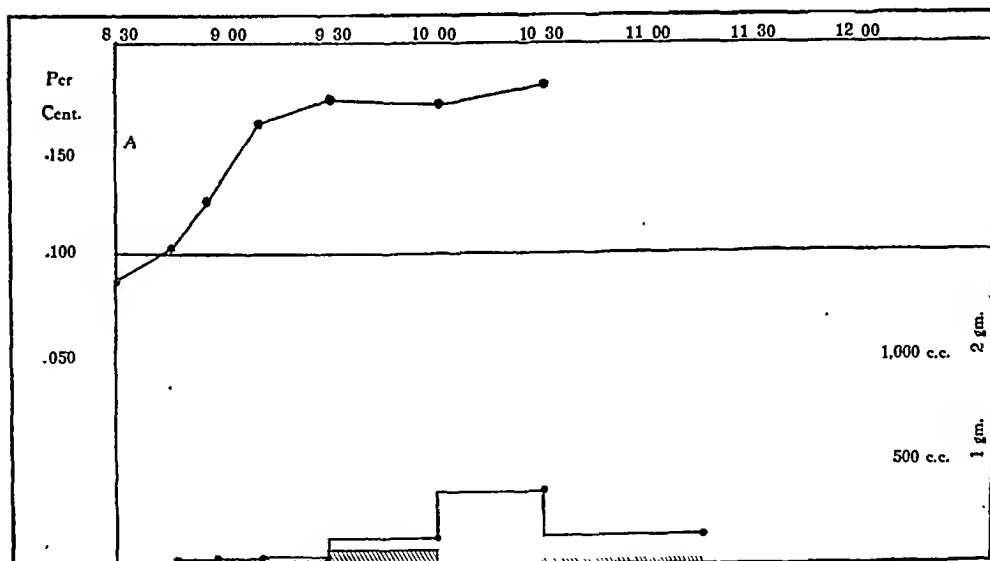


Chart 12 (Case 24).—A diabetic type of reaction in a patient with Graves' disease. The rise is moderately abrupt, the high point being reached in a little less than one hour after the administration of glucose. There is a marked plateau, for the blood sugar shows no tendency to fall two hours after the administration of glucose. The threshold fixed beautifully at about 0.175 per cent. When the blood sugar reaches 0.174 per cent. there is just a trace of sugar in the urine. In the period from 9:30 to 10 o'clock a little more sugar is excreted; so it is altogether probable that after 9:30 the blood sugar went a little higher. In the period from 10 to 10:30, when the blood sugar is between 0.17 per cent. and 0.18 per cent. no sugar is excreted. Following the period when the blood sugar reaches 0.18 per cent. a trace of sugar again appears in the urine. During the period from 10 to 10:30 there is a marked diuresis, which may have obscured a slight trace of sugar. A, glucose, 100 gm. in 500 c.c. of water.

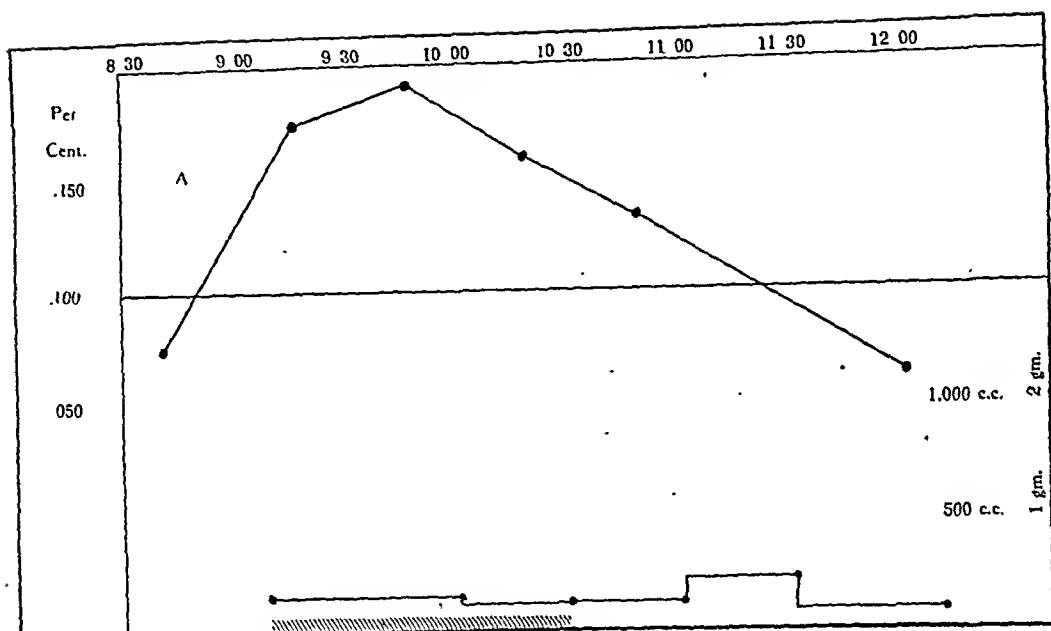


Chart 13 (Case 25).—A slight leaning toward the diabetic type of reaction in a patient with hyperthyroidism. The rise is rather abrupt, the high point being reached one hour after the administration of the glucose. There is no plateau. The fall is rather slow, the whole reaction lasting two and three-quarters hours. The blood sugar reached 0.19 per cent. as the highest point, and only a small amount of sugar is excreted in the urine. The threshold, therefore, both on the rise and on the fall must be somewhere in the neighborhood of 0.18 per cent. There is nothing remarkable about the diuresis. A, glucose, 100 gm. in 500 c.c. of water.

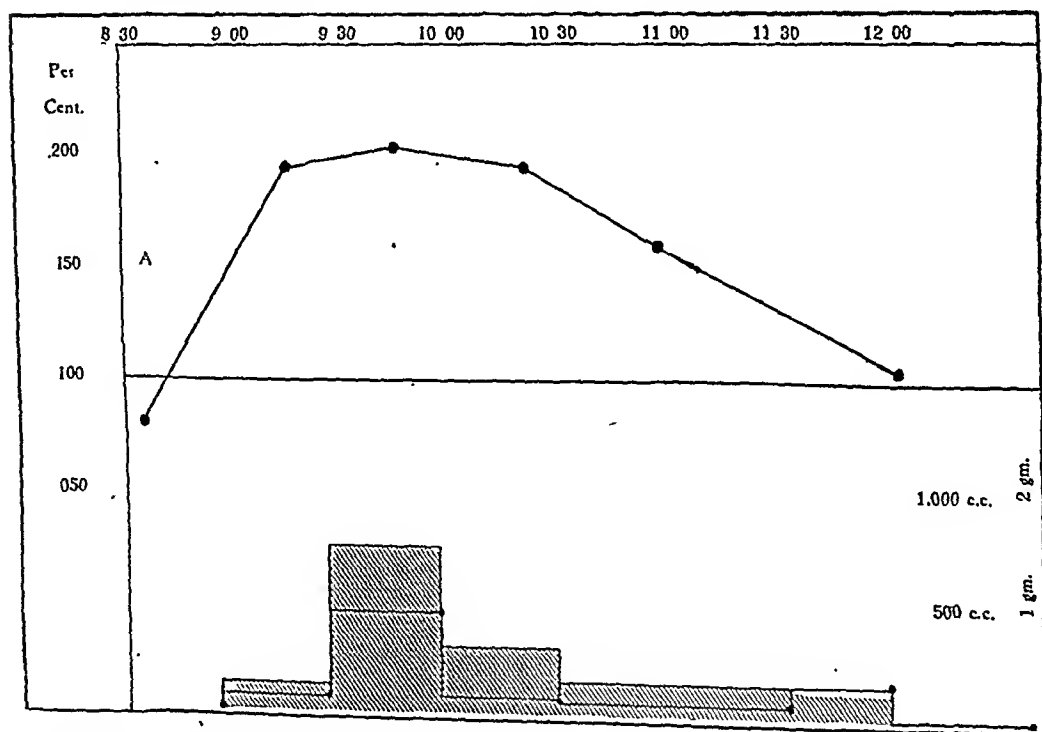


Chart 14 (Case 29).—A diabetic type of reaction in a patient with dys-pituitarism. The curve rises rather abruptly, the high point being reached one hour after the ingestion of 100 gm. of glucose. The curve is flattened at the summit and the decline is slow, the whole reaction lasting over three hours. The renal threshold was below 0.19 per cent. on the up-limb; it fell below 0.15 per cent. on the down-limb. There was a marked diuresis during the period of greatest glycosuria. A, glucose, 100 gm. in 300 c.c. of water.

TABLE 20.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 27

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:20	0.096	16	0
8:30	Glucose, 100 gm. in 300 c.c. water		
9:00	0.124	21	0
10:05	0.103	19	0
10:30	0.101	33	0
11:00	0.101	20	0
12:00	0.086	16	0

CASE 28 (Hospital No. 38977).—Diagnosis: cerebellar cyst. D. E., W. F. S., aged 16, gave a history of illness which began at 10 years, with headache, followed by gradual loss of vision. The patient was blind for two years. There was frequent vomiting with headache. Convulsions began during the second year of illness, and about the same time the patient began to have difficulty in walking. Additional symptoms were: loss of smell, failure of memory, irritability, marked gain in weight and absence of menstruation. The essential results of examination were: fairly well developed, rather fat; hypertrichosis; head large, suggesting internal hydrocephalus; divergent strabismus; slight ptosis on left; slight nystagmus to left; total blindness due to optic atrophy, and marked ataxia. The roentgen-ray examination revealed entire sella region obscured, probably destroyed, suggesting a growth in that region. There was marked evidence of intracranial pressure. The left cerebellar cyst was evacuated by operation Jan. 25, 1916. The glucose tolerance test was made Jan. 17, 1916. The protocol of this test is given in Table 21.

TABLE 21.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 28

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:20	0.108		
9:25	Glucose, 100 gm. in 300 c.c. water		
9:45	0.126	138	0
10:45	0.171		
10:58	*100	1.79
11:55	0.173		
12:20	50	1.97
12:45	0.126		
4:20	105	0

* Some urine voided involuntarily in bed.

CASE 29 (Hospital No. 40109).—Diagnosis: hypophysial tumor; cyst of chiasm. P. R., W. F. S., aged 32, gave a history of symptoms which began two years before admission to the hospital, with difficulty in urination and dull headache. The hands and feet grew larger. Two attacks of sudden blindness occurred with as sudden recovery. On admission, May 4, 1916, examination showed a well nourished woman; face broad, features masculine, maxillary prognathism; marked hypertrichosis; hands broad and fingers short; visual fields constricted; complete bitemporal hemianopsia and infantile pelvic organs. The roentgen-ray examination revealed acromegalia. An operation was performed June 5, 1916, for evacuation of infundibular cyst. The glucose tolerance test was made May 24, 1916. The data of this test are presented in Chart 14:

CASE 30 (Dispensary No. 52670).—Diagnosis: paralysis agitans; acromegalia. A. S., W. F. W., aged 60, came for relief of long standing constipation. Examination showed a well nourished woman with tendency to obesity; mask-like expression; muscular rigidity; characteristic tremor of hands; head large; massive features; wide separation of teeth, and spade-like hands. Roentgen-ray examination revealed large sella, thickened skull and phalanges, thickened and tufted. The glucose tolerance test was made March 2, 1916. The data of this test are presented in Chart 15.

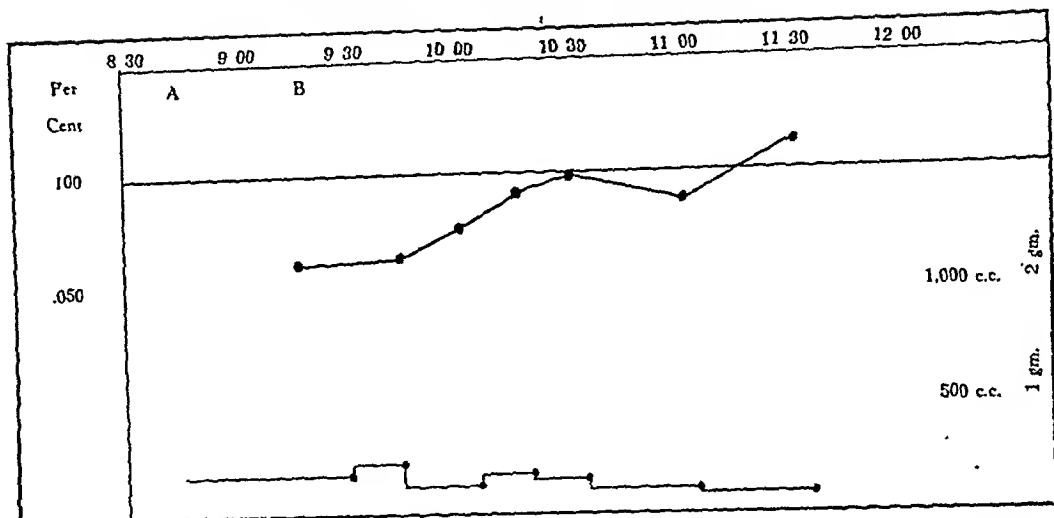


Chart 15 (Case 30).—Increased tolerance for carbohydrate in a patient with dyspituitarism. The blood sugar, to begin with, was quite low. The rise was slow, but after once reaching its high point, this high point was well sustained. There was a gradual elevation of the blood sugar from the time the experiment was begun until it was concluded, a period of two hours. There was a moderate diuresis which gradually fell throughout the experiment. A, voided; B, glucose, 100 gm. in 300 c.c. of water.

CASE 31 (Dispensary No. F. 50445).—Diagnosis: disturbance of endocrine glands (hypophysis (?) interrenal body (?)). M. G., W. M. S., aged 18, complained of swelling and cyanosis of hands, most marked in winter. Examination showed a rather short, well nourished but not obese boy; head large, and all features massive; ears large, high placed and standing out prominently; maxillary prognathism; anteroposterior bowing of spine; breasts large, with well developed nipples; absence of axillary hair; scant pubic hair, with transverse arrangement; hypospadiā; undescended left testicle and hands greatly enlarged from edema and extremely cyanotic. Roentgen-ray examination revealed periarticular swelling of hands, but no bone changes, enlargement of vessels of anterior skull region and normal sella, although unusual in shape. The glucose tolerance test was made March 20, 1916. The patient fasted. The protocol of this test is given in Table 22. The epinephrin test was made April 17, 1916, the data of which are presented in Chart 22.

TABLE 22.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 31

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:35	0.109		
8:42	Glucose, 100 gm. in 300 c.c. water		
8:44		70	0
8:55	0.122	921	0
9:10	0.132	632	0
9:30	0.137	960	0
9:49	0.111	677	0
10:27	0.103	246	0
11:28	0.109	135	0

CASE 32 (Hospital No. 36128).—Diagnosis: dyspituitarism (?). T. A., W. M. M., aged 38, gave a history of onset of symptoms occurring three years before admission, with a convulsion. Since then convulsions occurred at long intervals. The patient grew dull and morose, and very irritable. There was a rapid gain in weight. The patient was impotent for three years. Examination, July 30, 1916, showed a large, well nourished man with no abnormality other than a mild hypertension of 170:90. The visual fields were normal.

The optic disks were normal. Roentgen-ray examination revealed normal sella. The Wassermann test in blood serum was negative. The glucose tolerance test was made July 7, 1917. The protocol of this test is given in Table 23.

TABLE 23.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 22

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:00	0.100		
9:01	Glucose, 100 gm. in 300 c.c. water		
9:15	0.124		
9:30	0.155	28	0
10:00	0.215	36	0.36
11:00	0.200	68	2.26

SUMMARY

The five patients with obvious hyperthyroidism showed a lowered sugar tolerance. The blood sugar curve has to some extent the high, sustained, prolonged features of the diabetic type. All five had glycosuria, but only one (Case 22) put out a large amount of sugar. Case 26 had only a slight glycosuria, although the blood sugar went above 0.2 per cent. The urine contained albumin and a few hyaline casts, indicating a mild nephritis, no doubt with renal impermeability to glucose. In this patient the sugar tolerance was more seriously disturbed than a study of the urine alone would indicate. Case 23, Chart 11, is of special interest on account of the improved sugar tolerance one month after operation. The young man (Case 27) with a large colloid goiter and no obvious symptoms of disturbed thyroid function gave a normal reaction. The two patients (Cases 28 and 29, Chart 14) with well marked symptoms of overfunction of the hypophysis both yielded typical diabetic types of blood sugar curves. The mildly acromegalic (Case 30, Chart 15) in the quiescent or underfunction stage, had an unusually low fasting blood sugar and only a slight rise after 100 gm. of glucose, indicating a high sugar tolerance. Finally the patients (Cases 31 and 32) with only suggestive symptoms of deranged hypophysial function gave, the one a normal reaction, save for the remarkable diuresis; the other the characteristic reaction of low glucose tolerance.

REACTIONS IN VARIOUS DISEASES

In concluding we wish to report the reactions in a few patients with various disorders. Briefly, the clinical features of each case and the results of the test are as follows:

CASE 33 (Hospital No. 35175).—Diagnosis: acute lobar pneumonia; syphilis of the central nervous system. S. R., W. M. S., aged 44, was treated in a psychiatric clinic in the spring of 1915 for paresis. The present illness came on acutely two days before admission, Dec. 14, 1915. It was a typical lobar pneumonia with the crisis on the fourth day. The glucose tolerance test was made Dec. 31, 1915. The protocol of this test is given in Table 24.

TABLE 24.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 33

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:55	0.101		
8:56	Glucose, 100 gm. in 300 c.c. water		
9:25	0.164	?	0
9:50	0.195	20	Present
10:10	0.172	464	0.1
10:35	0.174	500	0.14
11:10	0.156	340	0.15
12:00	211	0

CASE 34 (Dispensary No. F-49930).—Diagnosis: emphysema; chronic bronchitis; asthma. M. E., W. M. M., aged 50, had had a cough, off and on, for fifteen years and dyspnea without definite attacks of asthma. The cough was most marked in late summer and early fall. Examination showed well marked emphysema, with sonorous and sibilant râles. The glucose tolerance test was made Jan. 27, 1916. The data of this test are presented in Chart 16.

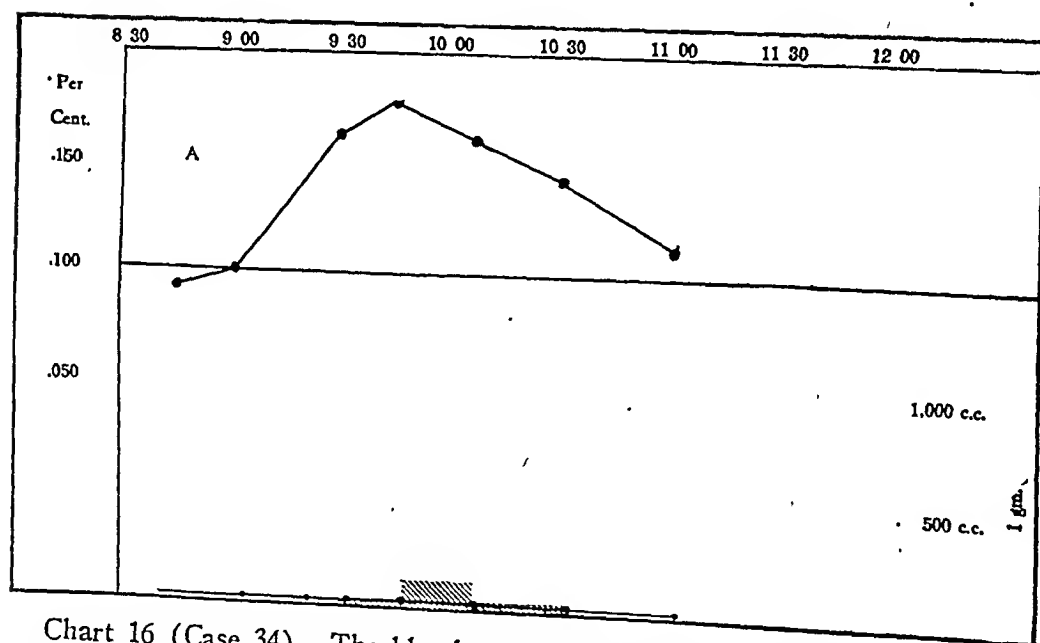


Chart 16 (Case 34).—The blood sugar rise, though relatively high, is fairly rapid, the high point being reached about fifty minutes after the administration of glucose. There is no plateau, and the fall is relatively rapid, the whole reaction being over in about two and one-half hours. The highest blood sugar is 0.178 per cent., and the patient puts out just a very small amount of glucose before this point is reached, so that the threshold on the rise is evidently a little above 0.17 per cent. On the fall the threshold is a little lower, for sugar is put out in the specimen collected at 10:33 and during the period from 10:06 to 10:33 the blood sugar falls from 0.16 to 0.145. There is no marked diuresis. At 6 a. m. the patient voided. A, glucose, 100 gm. in 310 c.c. of water.

CASE 35 (Hospital No. 35268).—Diagnosis: acute tonsillitis. H. H., W. M. S., aged 16, came to the hospital because sugar had been found in the urine. Except for mild tonsillitis, the boy was otherwise normal. During three weeks' stay in the hospital, sugar was never found in the urine. The glucose tolerance test was made Jan. 24, 1916. The protocol of this test is given in Table 25.

TABLE 25.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 35

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:45	0.098		
8:46	Glucose, 100 gm. in 300 c.c. water		
9:03	0.124	107	0
9:16	0.146	88	0
9:30	0.172	136	0
9:45	0.178	200	0
10:00	0.182	152	0
10:33	0.176	163	0
11:05	0.141	127	0
11:55	0.144	97	0

CASE 36 (Hospital No. 21835).—Diagnosis: chronic pelvic inflammatory disease. E. P., W. F. M., aged 22, entered the gynecologic service of the hospital for a pelvic operation. A small amount of sugar was found in the urine which at once disappeared on dietary restriction and did not reappear on the regular ward diet. The glucose tolerance test was made Jan. 31, 1916. The protocol of this test is given in Table 26.

TABLE 26.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 36

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30			
8:35	Glucose, 50 gm. in 200 c.c. water		
9:00	0.132		
9:15	192	0
9:30	0.168		
9:45	220	0
10:00	0.152		
10:15	416	0
10:30	0.098		
10:45	368	0
11:00	0.088		
11:15	380	0

CASE 37 (Hospital No. 35436).—Diagnosis: acute rheumatic fever; otitis media; syphilis (Wassermann); chronic tonsillitis. E. W., B. M. S., aged 24, was in the hospital with acute rheumatic fever in January, 1916. There was a return of symptoms shortly after discharge. The patient was readmitted Feb. 2, 1916. Physical examination disclosed pyorrhea alveolaris; chronic tonsillitis; genital scar, and swelling and redness of many joints. The Wassermann reaction was + + + +. The patient made a rapid recovery after administration of salicylates. The glucose tolerance test was made Feb. 14, 1916. The protocol of this test is given in Table 27.

TABLE 27.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 37

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
6:30	*Breakfast		
8:35	0.098	122	0
8:52	Glucose, 100 gm. in 300 c.c. water		
9:20	0.111	92	0
9:40	0.114	66	0
10:00	0.109		
10:20	0.095	68	0
11:05	0.096	49	0

*Small piece toast, small piece butter, oatmeal with sugar.

SUMMARY

The patient with general paresis (Case 33) convalescing from pneumonia, and the patient (Case 34, Chart 16) with asthma, showed a moderate decrease in carbohydrate tolerance; both excreted a little sugar after the administration of 100 gm. of glucose. The patient (Case 35) sent into the hospital as a diabetic on account of occasional glycosuria, showed a rather high and a definitely prolonged reaction without glycosuria. The test suggested only a little disturbance of sugar tolerance, and even on a very liberal general diet the patient never had glycosuria while in the hospital. The patient (Case 36) from the gynecologic service was investigated also on account of transient glycosuria. Except for being somewhat high, the curve is otherwise normal, and subsequently sugar was not again found. The patient (Case 37) with rheumatic fever was having an afternoon elevation of temperature up to 101 at the time the test was made; he had only a very slight rise of blood sugar after taking 100 gm. of glucose.

II

EPINEPHRIN HYPERGLYCEMIA

Our knowledge of the effects of epinephrin on carbohydrate metabolism in man has been gained chiefly from studies on epinephrin glycosuria. There are available only scant data about its effect on blood sugar and these data consist of single blood sugar determinations or at most of a few determinations at irregular intervals.⁸ Our studies with epinephrin were begun to discover the renal threshold for glucose in normal persons, and were then extended to confirm some interesting preliminary observations. The method employed was to give 50 gm. of glucose in the morning after the night fast and to follow this in from one-half to one hour with a subcutaneous injection of from 0.66 mg. to 1 mg. of epinephrin. The blood sugar, the blood pressure, the diuresis, the glycosuria and the general symptoms were studied at short intervals after the injection.

EPINEPHRIN REACTION IN NORMAL PERSONS

We have records of the epinephrin reaction in seven healthy persons (Case 1, Chart 17; Case 2, Chart 18; Case 3; Case 38, Chart 19; Case 40, Chart 23; Case 41, Chart 26). Data pertaining to Cases 1, 2 and 3 have already been given; those pertaining to Cases 38, 39, 40 and 41 are briefly as follows:

CASE 38.—S. W., W. M. M., healthy physician, aged 35, was given the epinephrin test Nov. 19, 1915. The data of this test are presented in Chart 19. There was a moderate general reaction; some palpitation and throbbing.

8. Bang: *Der Blutzucker*, Weisbaden, 1913, p. 85. Landau: *Ztschr. f. klin. Med.*, 1914, 79, 201.

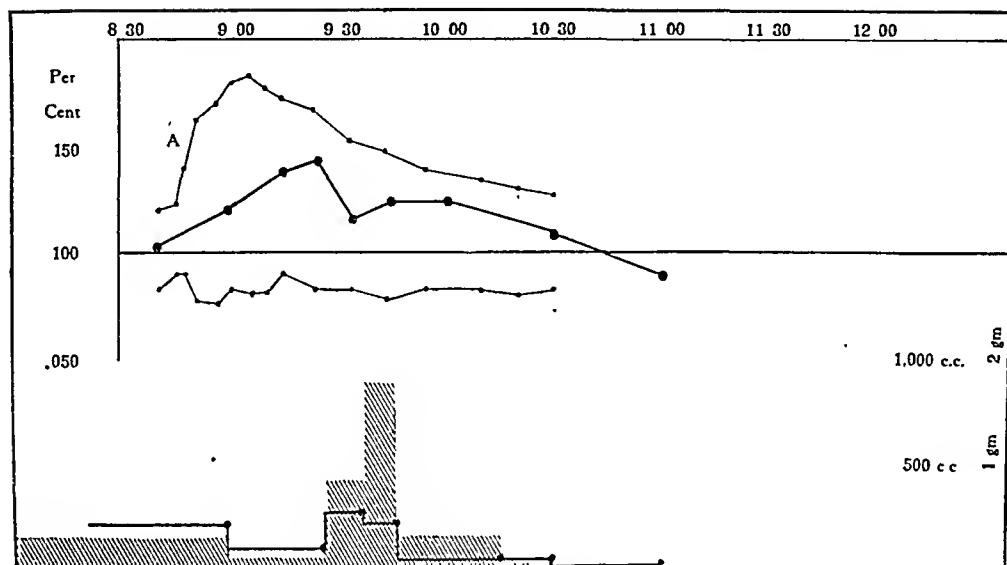


Chart 17 (Case 1).—A normal blood sugar reaction after epinephrin, with a low renal threshold. This chart offered much difficulty in interpretation, because the urine passed shortly after the administration of epinephrin, when the blood sugar was 0.12 per cent., showed more sugar than the following specimen collected during the period when the blood sugar rose from 0.12 per cent. to 0.14 per cent. The only possible explanation was that the patient had alimentary glycosuria after the administration of 50 gm. of glucose. For this reason he was tested by administering 50 gm. of glucose on an empty stomach, and glycosuria did occur. As the chart shows, the renal threshold is very low; it is certainly below 0.14 per cent. and in all probability in the neighborhood of 0.13 per cent. on the rise. When sugar excretion is started the threshold drops off still further, so that the patient continues to put out sugar, even when the blood sugar has fallen down to 0.108 per cent. The rise in the curve is rapid, the highest point being reached forty minutes after the administration of epinephrin. There is practically no plateau, for the blood sugar then rapidly falls off and has reached its original level after two hours and fifteen minutes. There is a well marked diuresis during the period of glycosuria, which again quickly subsides. During the period of the experiment 1.3 gm. of sugar are excreted. The blood pressure reaction is moderate. Patient complained of moderate throbbing and palpitation. At 7:15 a. m. the patient received 50 gm. of glucose in 500 c.c. of water. A, epinephrin, 1 mg.

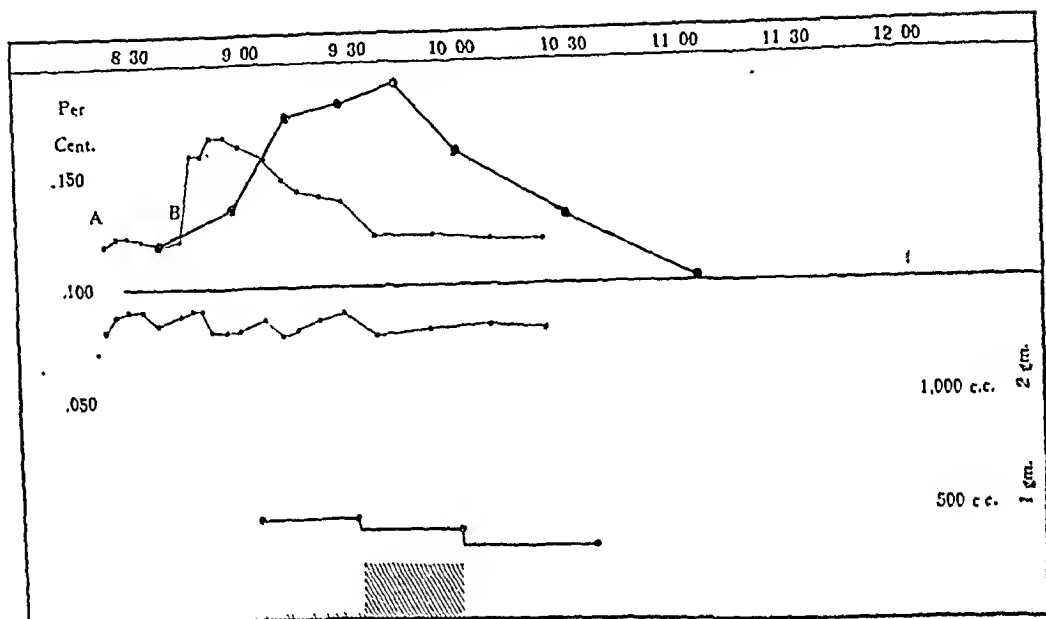


Chart 18 (Case 2).—An epinephrin reaction in a normal person. The blood sugar curve rises rapidly, the high point being reached an hour after the administration of epinephrin. There is no plateau. The blood sugar falls off abruptly from the high point and the whole reaction is over in a little less than two hours. The specimen of urine collected two minutes after the blood sugar reached 0.182 per cent. contains just a trace of sugar. The renal threshold, therefore, is a little below 0.18 per cent. There is nothing remarkable about the diuresis. During the period of the experiment 0.23 gm. of glucose is excreted. Marked subjective symptoms after the administration of epinephrin; marked throbbing and palpitation. The heart action extremely irregular due to numerous premature beats. Patient complained also of dryness of the mouth. At 7:30 a. m. the patient received 50 gm. of glucose in 1,000 c.c. of water. A, atropin, $\frac{1}{60}$ grain; B, epinephrin, 1 mg.

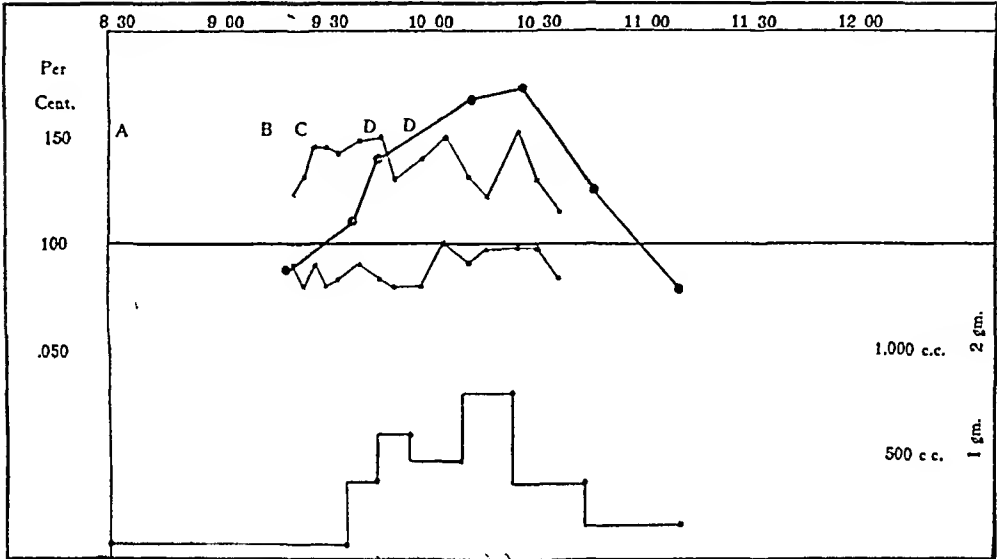


Chart 19 (Case 38).—A characteristic epinephrin reaction with moderate blood pressure and moderate blood sugar reaction. The blood sugar curve rises rapidly, the highest point being reached about thirty minutes after the administration of the epinephrin. There is no plateau. The blood sugar falls rapidly, and the whole reaction is over in less than two hours. It would appear that the threshold on the up-curve is somewhere between 0.14 per cent. and 0.15 per cent.; however, on the down-curve no sugar is excreted after the blood sugar has reached 0.173 per cent. Therefore, it is altogether probable that on the rise the blood sugar must have mounted to a higher point than is indicated on the chart during the interval between the specimens taken at 9:46 and 10:11. Therefore, the threshold is between 0.17 per cent. and 0.18 per cent. The diuresis is extremely marked. It is true the patient did drink some water in the early part of the experiment, but this would hardly account for the whole of the marked diuresis. The patient excreted only traces of sugar. Following the administration of epinephrin the patient complained of disagreeable throbbing in the abdomen and in the vessels of the neck. *A*, glucose, 50 gm. in 500 c.c. of water; *B*, water, 240 c.c.; *C*, epinephrin, 1 mg.; *D*, water, 120 c.c.

CASE 39.—D. T. B., W. M. S., healthy medical student, aged 24, was given the epinephrin test, June 15, 1916, the atropin-epinephrin test, June 16, 1916, and the pilocarpin-epinephrin test, June 18, 1916. The protocols of these tests are given in Tables 28, 29 and 30, respectively.

TABLE 28.—PROTOCOL OF EPINEPHRIN TEST IN CASE 39

Hour	Blood Sugar, Per Cent. Glucose, 50 gm. in 300 c.c. water	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30	0.135	60	0
9:00	Epinephrin, 0.66 mg.		Trace
9:02	0.195	420	1.72
9:20	0.205	750	1.05
10:00	0.146	192	0
10:30	0.103	90	0
11:00	0.092	50	0
11:30			

TABLE 29.—PROTOCOL OF ATROPIN-EPINEPHRIN TEST IN CASE 39

Hour	Blood Sugar, Per Cent. Glucose, 50 gm. in 300 c.c. water	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30			
8:45	Atropin, 1/60 gr.	60	0
9:00	0.102		
9:02	Epinephrin, 0.66 mg.		0
9:30	0.124	116	0
10:00	0.115	580	0
10:30	0.095	120	0
11:00	0.090	98	0
11:30	0.086	78	0

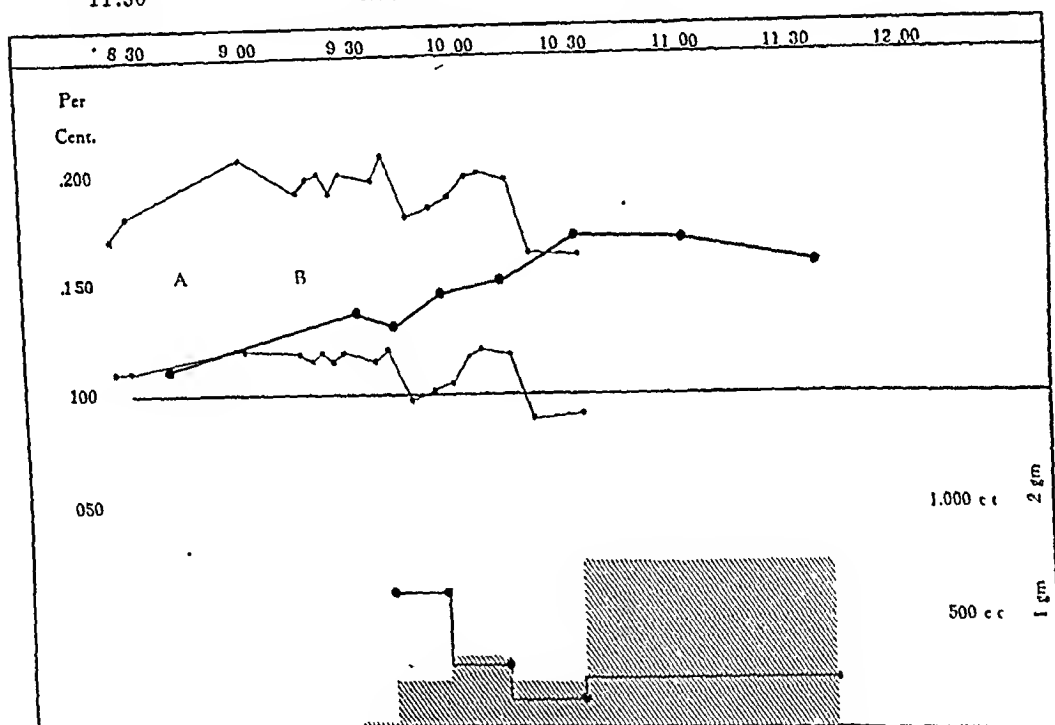


Chart 20 (Case 12).—A characteristic diabetic blood sugar chart, following the administration of epinephrin. The rise is slow, the highest point being reached one hour and fifteen minutes after the administration of epinephrin. The plateau is sustained. The blood sugar is just beginning to drop two hours and twenty minutes after the administration of epinephrin. The threshold on the rise is fixed accurately at 0.14 per cent. There is an initial or early diuresis following the administration of epinephrin; but during the period of glycosuria the diuresis rapidly falls. The total sugar excretion cannot be estimated because the experiment was broken off during the period of most marked glycosuria. The patient had moderate hypertension, and there is only a slight blood pressure reaction following the epinephrin. The initial rise of blood pressure followed catheterization undertaken to facilitate the collection of urine specimens. At 6:30 a. m. the patient received a carbohydrate free breakfast. A, water, 300 c.c.; B, epinephrin, 10 mg.

TABLE 30.—PROTOCOL OF PILOCARPIN-EPINEPHRIN TEST IN CASE 30

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:28	Glucose, 50 gm. in 300 c.c. water		
8:45	Pilocarpin, 1/10 gr.		
9:00	0.131	72	0
9:02	Epinephrin, 0.66 mg.		
9:30	0.160	240	0
10:00	0.172	430	0
10:30	0.140	144	0
11:00	0.112	72	0
11:30	0.092	40	0

CASE 40.—A. H. B., W. M. S., healthy medical student, aged 23, was given the epinephrin test, June 21; the atropin-epinephrin test, June 22, and the pilocarpin-epinephrin test, June 23, 1916. The data of these tests are presented in Charts 23, 24 and 25, respectively.

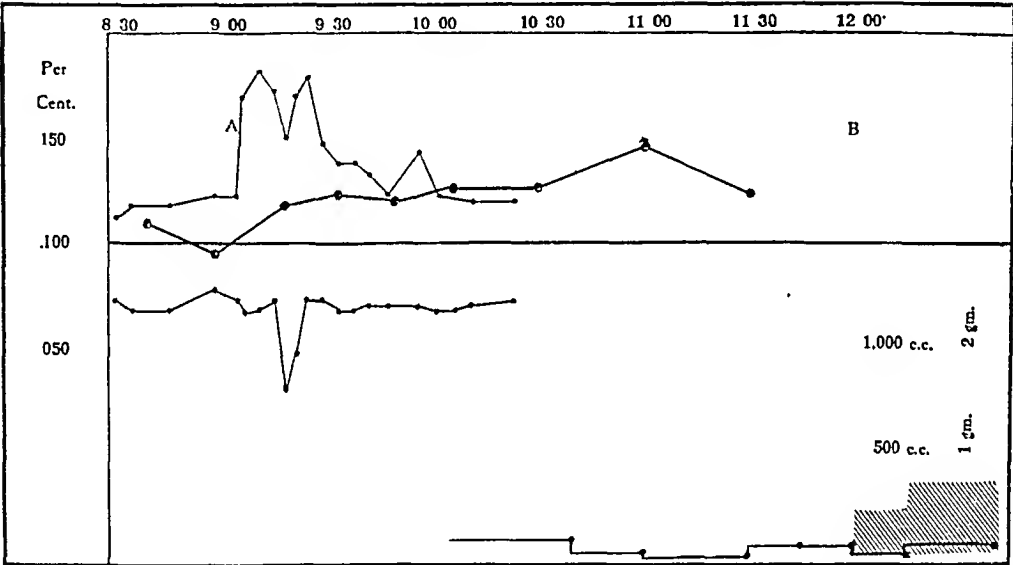


Chart 21 (Case 24).—This chart is a striking contrast to Chart 6, portraying the alimentary test in the same patient. Although there is an extreme blood pressure reaction after epinephrin, the blood sugar does not rise as high as in the alimentary test. However, although the blood sugar rises only moderately and very slowly, the rise is well sustained. Two and a half hours after the administration of epinephrin the blood sugar has not yet come down to its original level. There is no diuresis; indeed, only a small amount of urine is excreted, a much smaller amount than following the alimentary test. At noon the patient ate his luncheon, and following this there is a marked alimentary glycosuria. As stated above, the blood pressure reaction after epinephrin was extreme. The patient was blanched, and after an attempt to pass urine the diastolic pressure fell to 30 mm. Hg. The patient almost fainted at this time; but it was remarked that in spite of his extreme pallor and faintness there was no sweating. At 8 a. m. the patient received 50 gm. of glucose in 500 c.c. of water; at 8:10 a. m., voided. *A*, epinephrin, 1 mg.; *B*, luncheon.

CASE 41.—N. B. H., W. M. S., healthy medical student, aged 23, was given the epinephrin test, June 28; the atropin-epinephrin test, June 29, and the pilocarpin-epinephrin test, June 30, 1916. The data of these tests are presented in Charts 26, 27 and 28, respectively.

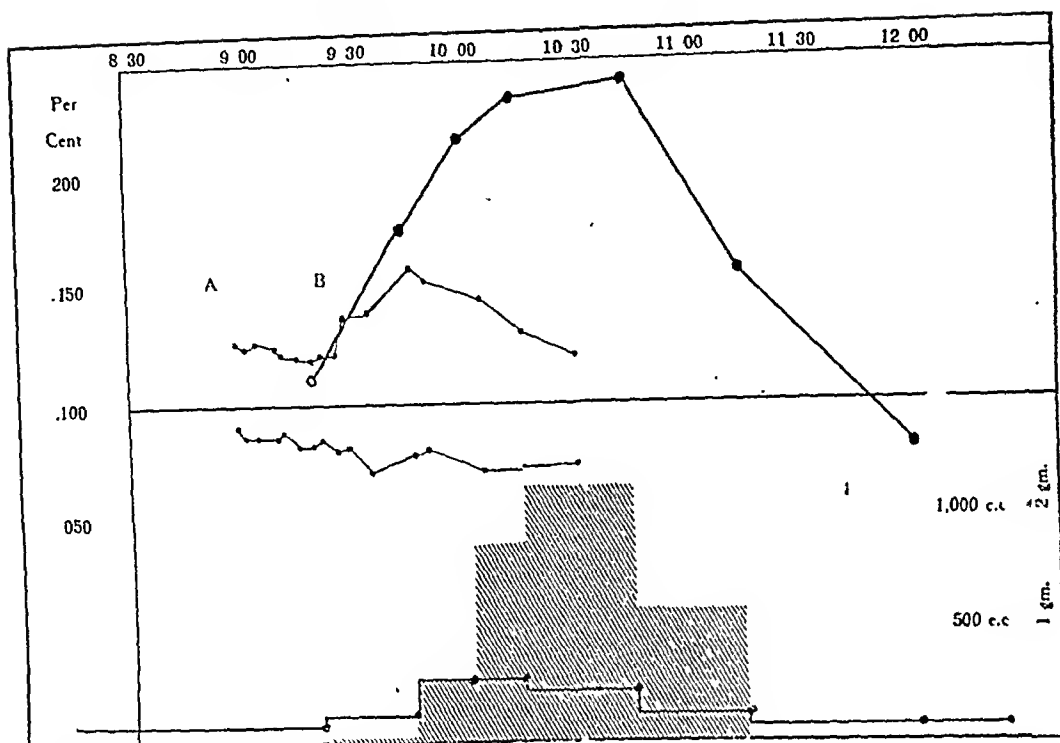


Chart 22 (Case 31).—A rather marked epinephrin reaction in a patient with symptoms suggesting dyspituitarism. The blood sugar rises rapidly, the high point being reached eighty minutes after administration of the epinephrin. The fall is still more abrupt, the whole reaction lasting about two hours. A bare trace of sugar is excreted in the specimen collected immediately after the blood sugar has reached 0.176 per cent. Therefore, the renal threshold is a little over 0.17 per cent. During the period of the experiment 3.7 gm. of glucose were excreted. There is moderate diuresis during the period of glycosuria. There is a moderate blood pressure reaction, but the patient complained of no unpleasant symptoms during the test, although moderate throbbing in the vessels was apparent. The heart's action showed marked sinus arrhythmia. At 7 a. m. the patient voided. A, glucose, 50 gm. in 300 c.c. of water; B, epinephrin, 1 mg.

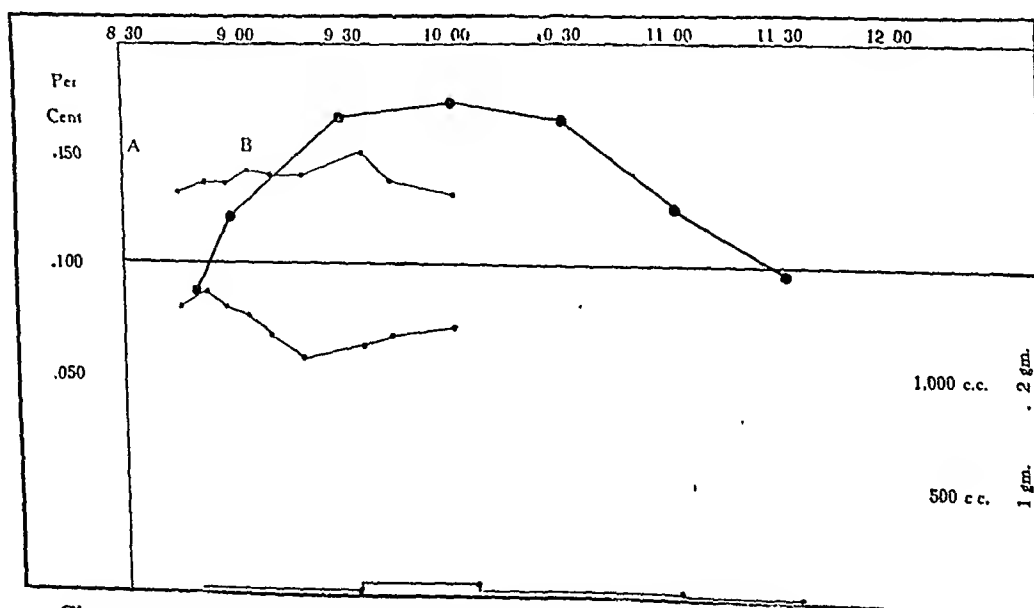


Chart 23 (Case 40).—Reaction after epinephrin. A, glucose, 50 gm. in 300 c.c. of water; B, epinephrin, 0.66 mg.

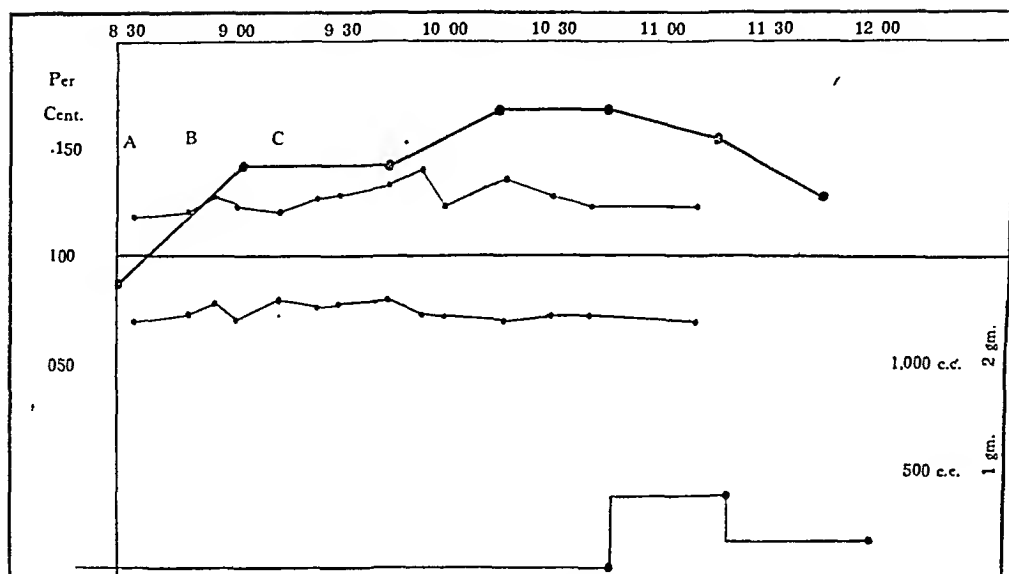


Chart 24 (Case 40).—Reaction after atropin and epinephrin. At 7:50 a. m. the patient voided. A, glucose, 50 gm. in 300 c.c. of water; B, atropin, $\frac{1}{60}$ grain; C, epinephrin, 0.66 mg.

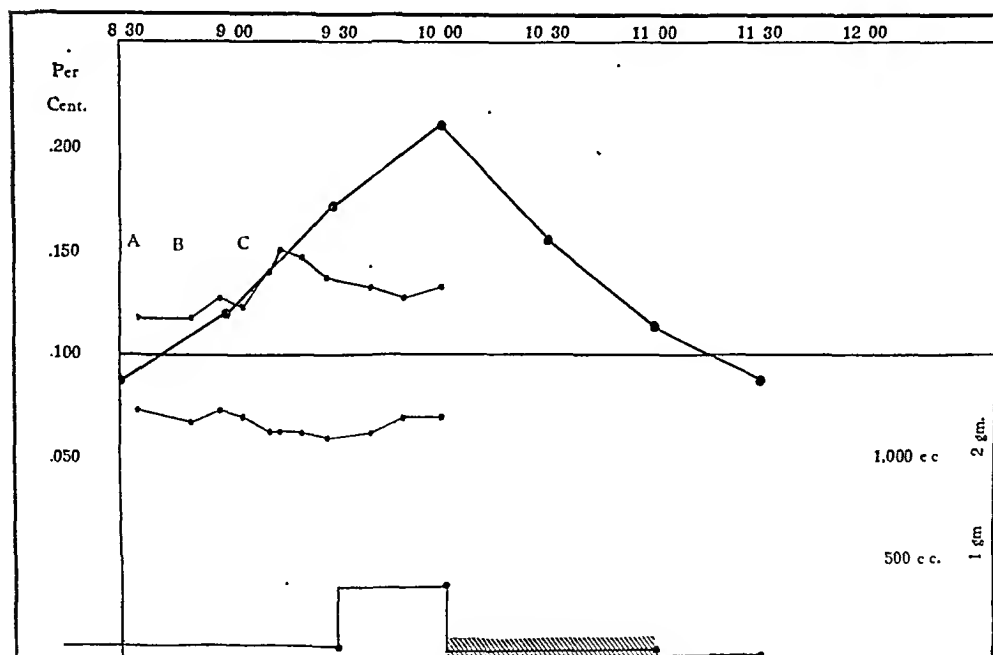


Chart 25 (Case 40).—Reaction after pilocarpin and epinephrin. At 7:50 a. m. the patient voided. A, glucose, 50 gm. in 300 c.c. of water; B, pilocarpin, $\frac{1}{40}$ grain; C, epinephrin, 0.66 mg.

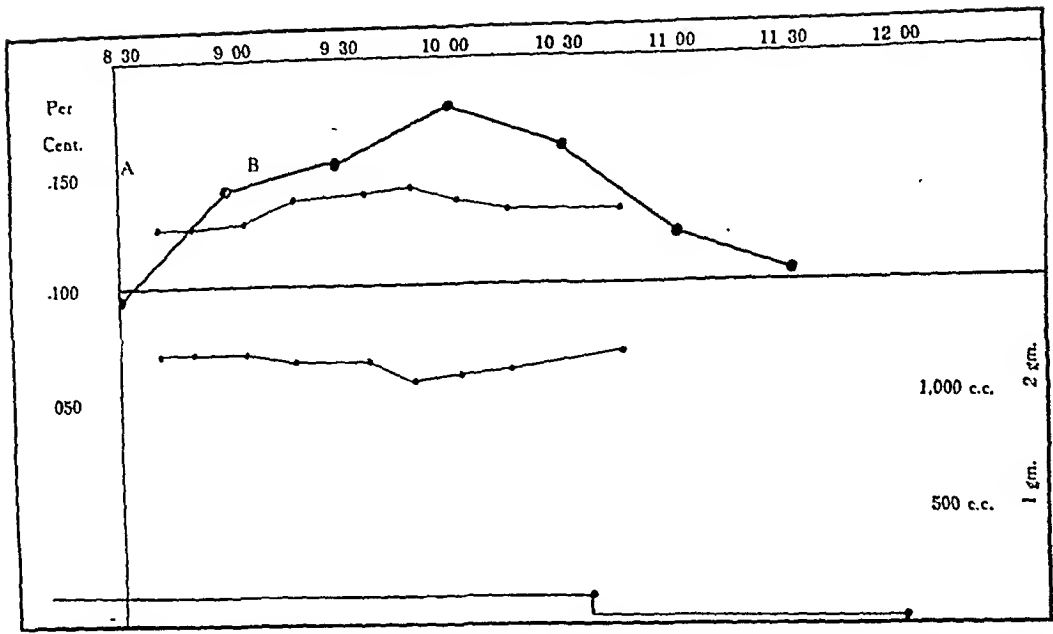


Chart 26 (Case 41).—Reaction after epinephrin. At 7:10 a. m. the patient voided. *A*, glucose, 50 gm. in 300 c.c. of water; *B*, epinephrin, 0.66 mg.

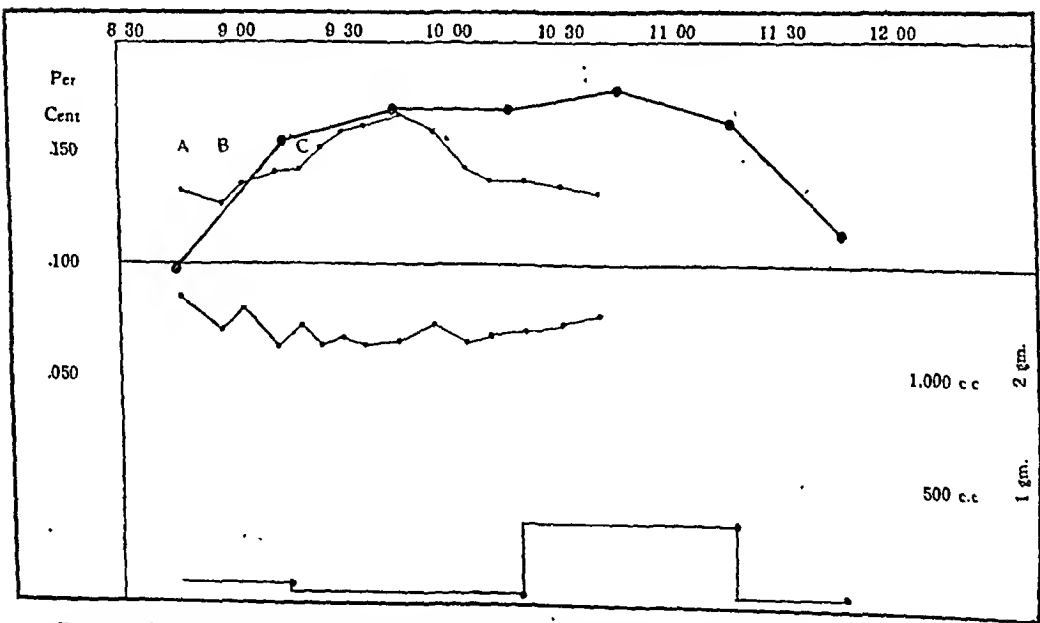


Chart 27 (Case 41).—Reaction after atropin and epinephrin. At 7:10 a. m. the patient voided. *A*, glucose, 50 gm. in 300 c.c. of water; *B*, atropin, $\frac{1}{60}$ grain; *C*, epinephrin, 0.60 mg.

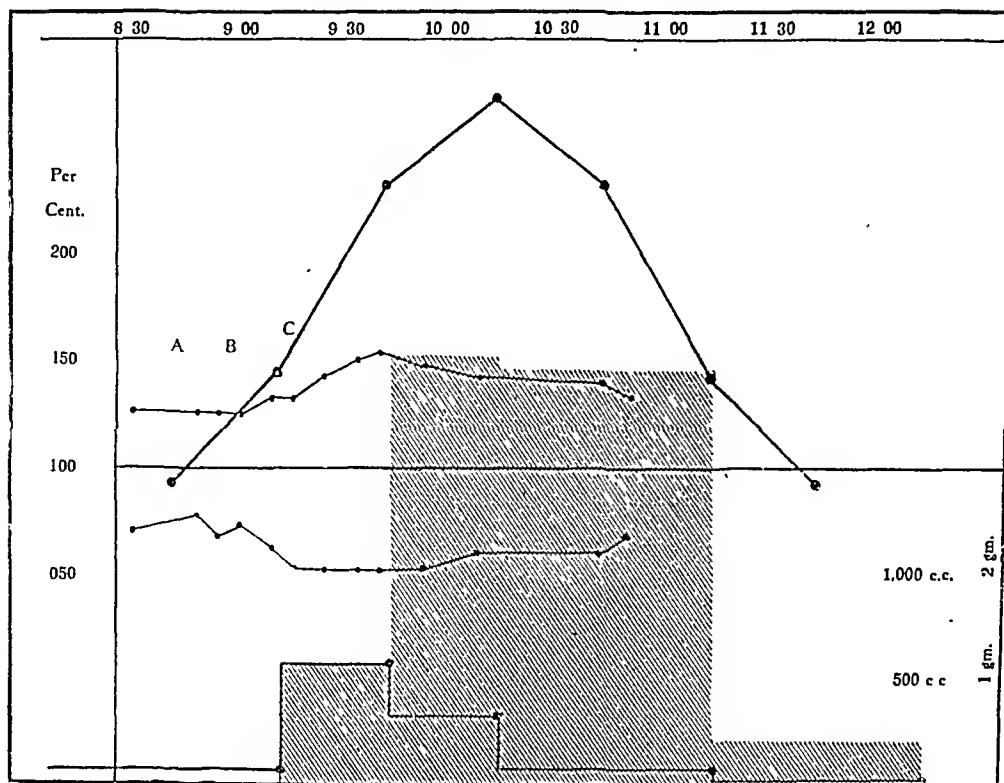


Chart 28 (Case 41).—Reaction after pilocarpin and epinephrin. At 7:15 a. m. the patient voided. *A*, glucose, 50 gm. in 300 c.c. of water; *B*, pilocarpin, $\frac{1}{10}$ grain; *C*, epinephrin, 0.66 mg.

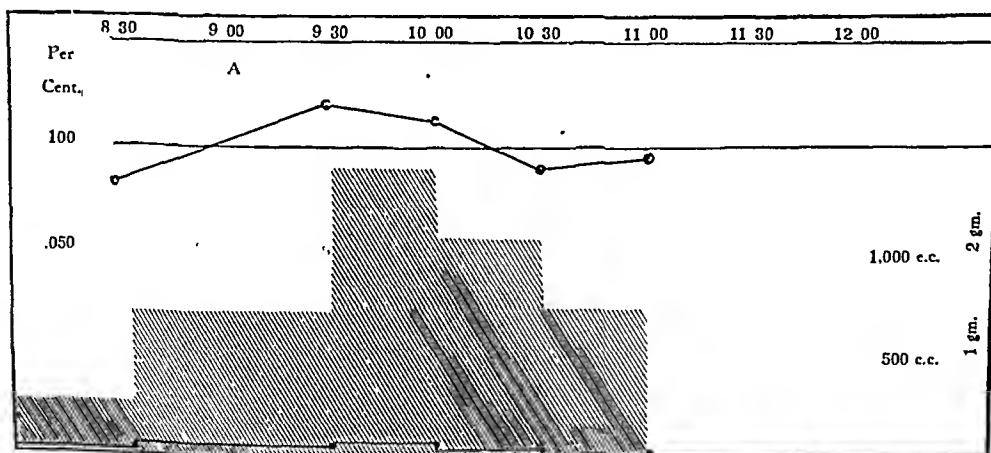


Chart 29.—Reaction in an unusually well marked case of renal diabetes. The blood sugar curve is altogether normal, the highest point, namely, 0.12 per cent., being reached within thirty minutes after taking 100 gm. of glucose, and the whole reaction being over in an hour and a half. However, there is a marked glycosuria in spite of the normal blood sugar curve. When the experiment was begun after the night fast the patient had considerable sugar in the urine, although the blood sugar was only 0.084 per cent. At 6 p. m. the patient had dinner; at 9 p. m., ate an ice cream cone, and at 8 a. m., voided. *A*, glucose, 100 gm. in 300 c.c. of water.

SUMMARY

Following the subcutaneous administration of epinephrin to normal persons, there was a prompt rise in the blood sugar, which reached its maximum in one hour and then rapidly subsided, the whole reaction being over in two hours. Sometimes the rise was a little quicker; sometimes it occurred somewhat more slowly, but the variations are small. Four persons receiving 1 mg. of epinephrin all had glycosuria varying from a trace of sugar to an excretion at the rate of 7.9 gm. per hour (Case 3). Of the three receiving 0.66 mg. of epinephrin only one had glycosuria. The occurrence of glycosuria and its degree ran parallel with the degree of hyperglycemia. The apparent exception to this statement (Chart 17) is interesting because this person, although normal in all other respects, had a low renal threshold. The threshold was low to the alimentary test as well as after epinephrin. All of our observations show that epinephrin has no influence on the renal threshold. The five persons with glycosuria had a more or less marked diuresis occurring principally during the period of sugar excretion. However, the diuresis was not always parallel with the glycosuria and as further observations showed there was sometimes a marked diuresis without glycosuria and sometimes a falling diuresis during the period of most marked glycosuria. Two of the patients with glycosuria (Cases 2 and 3) had previously had alimentary tests and neither gave unusual reactions; indeed, Case 3 showed only a slight rise in the blood sugar after 100 gm. of glucose, whereas, after epinephrin he had an extreme hyperglycemia and glycosuria. There was no correspondence whatsoever between alimentary hyperglycemia and epinephrin hyperglycemia. All seven persons had a mild or a moderately severe blood pressure reaction and the general symptoms ran parallel with the degree of blood pressure response, consisting of unpleasant palpitation and throbbing, of a little nervousness and headache, and in one instance also of chilliness and blanching of the skin. There is no correspondence between the degree of blood pressure response or the severity of the general symptoms and the degree of hyperglycemia. As we shall later show, atropin often greatly increases the blood pressure effect of epinephrin, whereas the hyperglycemia is thereby diminished.

EPINEPHRIN REACTIONS IN VARIOUS DISEASES

We have studied the epinephrin reaction in various diseases and state briefly the main clinical features and the results of the test in those cases not already cited (Case 12, Chart 20; Case 24, Chart 21; Case 31, Chart 22; Cases 42, 43, 44 and 45).

CASE 42 (Hospital No. 34891).—*Diagnosis*: acute rheumatic fever. A. S., W. M. M., aged 33, gave a history of three previous hospital admissions for

acute rheumatic fever. The patient was otherwise healthy, except that he had always been a nervous man. The present admission, March 4, 1915, was for another attack of rheumatism. The patient had a mild attack without complications. The epinephrin test was made Nov. 15, 1915. The protocol of this test is given in Table 31.

TABLE 31.—PROTOCOL OF EPINEPHRIN TEST IN CASE 42

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:45	0.085		
	Glucose, 50 gm. in 400 c.c. water		
8:45	0.101		
9:15	0.092		
9:30	Epinephrin, 1 mg.		
9:32	0.137	900	0
9:45	0.182	408	0.53
10:05	0.218	90	2.16
10:25	0.209		
10:45	0.150	208	1.0
11:00		1350	0
11:15			

CASE 43 (Hospital No. 34996).—Diagnosis: syphilis; syphilitic periostitis; secondary anemia. J. H., B. M. S., aged 25, gave a history of irregular general symptoms for eight months; headache, general pains and weakness. Examination on admission to the hospital Nov. 8, 1915, showed general glandular enlargement, points of tenderness over elbow, ribs and cervical and lumbar spines. The Wassermann reaction was + + + +. The epinephrin test was made Dec. 8, 1915. The protocol of this test is given in Table 32.

TABLE 32.—PROTOCOL OF EPINEPHRIN TEST IN CASE 43

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
7:30	Glucose, 50 gm.		
8:45	0.098		
9:13	Epinephrin, 1 mg.		
9:29	0.117	50	0
9:45	0.128	90	0
9:58	0.146	162	0
10:15	0.141	90	0
10:45	0.119	250	0
11:15	0.120	50	0

CASE 44 (Hospital No. 34983).—Diagnosis: carcinoma of prostate; cystitis; myocardial insufficiency; carcinoma of bones (metastases); acute fibrinous pleurisy; acute fibrinous pericarditis. P. N., B. M. M., aged 57, had a sharp pain in lower back in April, 1915. Soon after the patient had difficulty in walking; frequent urination and difficulty in urination, and edema of the legs. On admission to the hospital, examination showed emaciation; anemia; cardiac enlargement; retention of urine; firm, hard prostate and metastases in bones. The phenolsulphonephthalein test was 64 per cent. There was a gradual downward course, ending in death, April 20, 1916. The anatomic diagnosis was essentially the same as the clinical. The epinephrin test was made Feb. 7, 1916. The protocol of this test is given in Table 33.

TABLE 33.—PROTOCOL OF EPINEPHRIN TEST IN CASE 44

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:00	0.100		
	Glucose, 50 gm. in 150 c.c. water		
9:06	0.108		
9:30	Epinephrin, 1 mg.	28	0
9:32	0.170		
9:45	0.195	26	0
10:02	0.210	180	0
10:15	0.205	4	0
10:30	0.149	6	0
10:48	0.141	25	0
11:00	0.117	125	0
11:58		37	0

CASE 45 (Hospital No. 35928).—Diagnosis: tuberculous peritonitis; pleurisy with effusion. L. J., B. M. S., gave a history of onset of symptoms in April, 1915, with pleurisy. A second attack of pleurisy occurred in June, 1915. The patient was well till December, 1915, when pleurisy came on again, followed by swelling of abdomen, loss of appetite and loss of weight. On admission to the hospital, Feb. 1, 1916, examination showed a poorly nourished colored man with considerable fever, pleurisy on both sides with effusion on right, ascites and epigastric mass. There was a gradual loss of fever and improvement in general condition. The epinephrin test was made Feb. 28, 1916. The protocol of this test is given in Table 34. The blood pressure rose from 122 and 78 to 178 and 86. The patient showed restlessness, palpitation and extrasystolic irregularity.

TABLE 34.—PROTOCOL OF EPINEPHRIN TEST IN CASE 45

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
6:00	Light breakfast		
7:30	Glucose, 50 gm. in 200 c.c. water		
8:52	0.081	145	0
9:09	Epinephrin, 1 mg.		
9:28	0.079	269	0
9:50	0.130	93	0
10:10	0.112	42	0
10:30	0.100	57	0
11:00	0.077	88	0
11:35	0.078	79	0

SUMMARY

In a general way these epinephrin reactions show the same features as were commented on in discussing the reaction in normal persons. Only two of the reactions deserve special consideration. However, a few differences may be pointed out. Case 31, Chart 22, is noteworthy on account of the well marked diuresis which, however, was not so marked as after the alimentary test even though following the alimentary test there was no glycosuria. The disproportion between the moderate blood sugar reaction after the alimentary test and the marked hyperglycemia and glycosuria after epinephrin also deserve attention. Case 42 is unusual in showing a falling diuresis during the period of most marked glycosuria. Case 44 had carcinoma of the prostate and urinary retention and showed, as was to be expected, renal impermeability; although the blood sugar rose to 0.21 per cent. only a trace of sugar appeared in the urine. Cases 43 and 45 are remarkable only on account of the slight blood sugar rise after 1 mg. of epinephrin. Both patients were colored men, and from our limited experience we are inclined to believe that the colored race shows less carbohydrate metabolism disturbance after epinephrin than does the white race.

The two epinephrin reactions deserving special comment are the reaction in a diabetic (Case 12, Chart 20) and the reaction in a patient with hyperthyroidism (Case 24, Chart 21). In the previous section we described the fundamental difference between the normal type and the diabetic type of reactions to the alimentary test. Both of these patients responded to the alimentary test with a high and very pro-

longed blood sugar curve, one (Case 12, Chart 5) with a low renal threshold, the other (Case 24, Chart 12) with a normal renal threshold. The important point we wish to emphasize now is that after epinephrin the same prolonged blood sugar curve was reproduced. The diabetic with a low renal threshold put out a large amount of sugar in the urine. The patient with hyperthyroidism and a normal renal threshold had less hyperglycemia after epinephrin than after the alimentary test, and since the blood sugar rose only to 0.15 per cent. no sugar flowed off in the urine. However, the alimentary hyperglycemia following luncheon, added to the epinephrin hyperglycemia, is followed by glycosuria. On an ordinary diet the patient never had sugar in the urine. The extreme blood pressure reaction, the marked cardiac irregularity and the severe general symptoms following epinephrin are also noteworthy.

EFFECTS OF ATROPIN AND PILOCARPIN ON EPINEPHRIN HYPERGLYCEMIA

Falta, Newburgh and Nobel⁹ state that atropin increases the glycosuric effect of epinephrin, whereas pilocarpin decreases it. Of four persons who had no glycosuria after the injection of epinephrin three became positive when the second injection was preceded by giving atropin for a few days. Two cases with glycosuria after epinephrin became negative when the second injection was preceded one-half hour by an injection of pilocarpin. These results fit in so well with the general facts established for the antagonistic action of autonomic and sympathetic nerves on smooth muscle and glands that we had no thought of questioning their correctness. The few preliminary observations we wish to report were made with the confident expectation that they would confirm in a striking way the results reported by Falta, Newburgh and Nobel. We were surprised to find that, according to our experiments, the facts are directly opposed to their assertions; for atropin, when it acts at all, diminishes the glycosuric effect of epinephrin, and pilocarpin, when it shows any decided influence, increases the glycosuric effect of epinephrin. Had we been better informed, our confidence might have been less complete and our results not so unexpected. Frank and Isaak¹⁰ were unable to confirm in dogs the observations made by Falta, Newburgh and Nobel in man. Doyon and Gautier¹¹ have shown that an injection of epinephrin causes a marked diminution in the glycogen content of the liver, and that this effect is greatly diminished if the epinephrin is preceded by an injection

9. Falta, Newburgh and Nobel: *Ztschr. f. klin. Med.*, 1911, **72**, 97.

10. Frank and Isaak: *Ztschr. f. exper. Path. u. Therap.*, 1910, **7**, 326.

11. Doyon and Gautier: *Compt. rend. Soc. de biol.*, 1908, p. 866.

tion of atropin into the bile duct. Doyon and Kareff¹² find that the injection of pilocarpin into a mesenteric vein causes a marked diminution in the glycogen content of the liver. Cavazzani and Soldaini¹³ conclude from their experiments that atropin paralyzes the nerves that stimulate the production of glycogen. From clinical observations, Rudisch¹⁴ is convinced that atropin diminishes the tendency to glycosuria in diabetes and he has warmly advocated the use of atropin in this disease. However, Mosenthal¹⁵ was unable to confirm his results.

Our observations on the effects of atropin and pilocarpin on epinephrin hyperglycemia are recorded in Case 2, Chart 18; Case 39; Case 40, Charts 23, 24 and 25; Case 41, Charts 26, 27 and 28.

In Case 2 following epinephrin the blood sugar rose to 0.174 per cent. and is accompanied by marked glycosuria, over 2 gm. of sugar being excreted during the experiment; in a second experiment when the epinephrin is preceded twenty minutes by the subcutaneous injection of atropin, 1/60 grain, the blood sugar rose to 0.19 per cent., but only a small amount of sugar, namely, 0.23 gm. came out in the urine. The discrepancy here between blood sugar and urine sugar would lead one to conclude that there had been a singular variation in renal permeability. However, a simpler explanation is quite likely to be the correct one. The first experiment is one of the earliest in our series, done when we were just beginning to use the Lewis-Benedict blood sugar method. After we became more experienced we discovered that our earlier readings were uniformly too low, due, we are sure, to insufficient or improper heating. The second experiment was done nearly six weeks after the first, at which time we had gained skill and assurance in our blood sugar technic. Therefore we believe that in this instance the urine sugars are more reliable than the blood sugars, and judged by this standard epinephrin alone had a greater effect on sugar mobilization than atropin and epinephrin together. This result is all the more striking when contrasted with the vascular reaction. Following epinephrin alone there was only a moderate blood pressure elevation and moderate palpitation and throbbing; after atropin and epinephrin the blood pressure reaction was twice as marked as after epinephrin alone, and the heart's action was very irregular from numerous premature beats accompanied by disagreeable palpitation and throbbing.

In the other three experiments smaller doses of epinephrin were employed than in Case 2, in order to avoid the unpleasant circulatory

12. Doyon and Kareff: *Compt. rend. Soc. de biol.*, 1908, p. 1056.

13. Cavazzani and Soldaini: Cited by Meyer and Gottlieb, *Pharmakologie*, 1911, p. 373.

14. Rudisch: *Jour. Am. Med. Assn.*, 1909, **53**, 1366.

15. Mosenthal: *Jour. Am. Med. Assn.*, 1912, **58**, 777.

symptoms that come after the use of atropin and epinephrin. The blood pressure reactions, therefore, do not stand out so prominently, but the blood sugar reactions are all the more striking.

In Case 39, after epinephrin the blood sugar went to 0.205 per cent. and considerable sugar was excreted in the urine; after atropin and epinephrin the blood sugar went only to 0.124 per cent. and no sugar appeared in the urine; after pilocarpin and epinephrin the blood sugar went to 0.172 per cent. without accompanying glycosuria. In this experiment epinephrin alone produced a more marked hyperglycemia than did epinephrin preceded by either atropin or pilocarpin; however, atropin diminished the epinephrin action far more than did pilocarpin.

The results in Cases 40 and 41 are portrayed in the accompanying charts, and need little further comment. In Case 40, after epinephrin alone the blood sugar went to 0.174 per cent. without glycosuria; after atropin and epinephrin to 0.168 per cent. without glycosuria; after pilocarpin and epinephrin to 0.21 per cent. with moderate glycosuria.

In Case 41, after epinephrin alone the blood sugar went to 0.178 per cent. without glycosuria; after atropin and epinephrin to 0.178 per cent. without glycosuria; after pilocarpin and epinephrin to 0.272 per cent. with marked glycosuria.

III

THE RENAL THRESHOLD FOR GLUCOSE

In making the studies reported in the two previous sections, we had as an important object the determination of the renal threshold for glucose. The data there recorded provides the basis for this section as well, and many of the charts were introduced mainly to illustrate the lessons we wish now to draw from them.

In spite of the importance of the question, no systematic studies of the renal threshold for glucose have been made. Such information as we possess rests mainly on a single blood sugar estimation, or at most on a few estimations at long intervals. For instance, one hour after the administration of glucose, or after the injection of epinephrin, a blood sugar estimation is made, and from this single observation the conclusion is drawn that that particular person does or does not excrete sugar at this level of blood sugar concentration. In this way it has been found that some healthy persons excrete abundant sugar with a blood sugar of 0.11 per cent.¹⁶ while others show no glycosuria with a blood sugar of 0.16 per cent. Since we now know that the blood sugar undergoes marked and rapid fluctuation after the ingestion of carbohydrate, after the administration of epinephrin, and after other procedures that influence its level, we

16. Liefman and Stern: *Biochem. Ztschr.*, 1906, **1**, 299.

realize that single blood sugar observations will only occasionally hit on the highest point of concentration.

However, in spite of the inadequacy of our information there has been ground enough for the prevalent opinion that the renal threshold is a variable factor. In nephritis, for instance, the renal permeability for glucose is often raised, and this alteration has been made the basis of a renal function test; in certain unusual instances of glycosuria spoken of as renal diabetes all the clinical symptoms are thought to depend on a decided lowering of the renal threshold; in diabetes the renal threshold is very inconstant, for many patients have glycosuria when the blood sugar is below 0.15 per cent., whereas others are

TABLE 35.—THE RENAL THRESHOLD IN CASES 1 TO 42, INCLUSIVE

Case Number	Age	Diagnosis	Renal Threshold, Per Cent.	Remarks
1	27	Normal	0.13 to 0.14	
	27	Normal	0.12 to 0.14	Epinephrin, Chart 17
2	33	Normal	0.16 to 0.17	
	33	Normal	0.17 to 0.18	Epinephrin, Chart 18
5	25	Normal	0.13 to 0.14	Chart 2
38	36	Normal	0.17 to 0.18	Epinephrin, Chart 19
7	40	Diabetes, mild	0.15 to 0.20	Chart 3
8	52	Diabetes, mild	0.17 to 0.20	
9	46	Diabetes, mild	0.17 to 0.19	Chart 4
10		Diabetes, mild	0.168 to 0.182	
11	25	Diabetes, moderately severe....	0.13 to 0.15	
12	61	Diabetes, moderately severe....	0.13 to 0.16	Chart 5
	61	Diabetes, moderately severe....	0.13 to 0.15	Epinephrin, Chart 20
13	33	Diabetes, moderately severe....	0.17 to 0.20	
	33	Diabetes, moderately severe....	0.17 to 0.18	Chart 16
14	39	Diabetes, severe	0.14 to 0.15	Chart 7
15	23	Diabetes, severe	0.178 to 0.182	Chart 8
16	49	Chronic diffuse nephritis.....	0.20 to 0.205	Chart 9
18	45	Chronic diffuse nephritis.....	0.17 to 0.18	Chart 10
44	57	Chronic diffuse nephritis.....	0.20 to 0.21	
23	52	Hyperthyroidism	0.16 to 0.176	Chart 11
24	17	Hyperthyroidism	0.17 to 0.18	Chart 12
25	31	Hyperthyroidism	0.168 to 0.185	Chart 13
26	51	Hyperthyroidism	0.19 to 0.20	
31	18	Dyspituitarism	0.17 to 0.176	Epinephrin, Chart 22
33	44	Lobar pneumonia, convalescent.	0.175 to 0.19	
34	50	Bronchial asthma	0.17 to 0.18	Chart 16
42	27	Acute rheumatic fever	0.16 to 0.19	Epinephrin

sugar free, or nearly so, with a blood sugar of 0.5 per cent. and over. These general facts have been known for a long time, but there are no detailed studies of the renal threshold in normal persons with which to compare the alterations produced by disease. As far as we know, only the observations of Jacobsen throw light on the subject. Jacobsen fed thirteen healthy persons 100 gm. of glucose, and at a second test 150 gm. of bread, and estimated the blood sugar at frequent intervals during the following two hours. None of those whose blood sugar remained below 0.16 per cent. had sugar in the urine, whereas, all but one of those whose blood sugar went above 0.17 per cent. did have glycosuria. He concludes, therefore, that in healthy persons the renal threshold for glucose is between 0.16 per cent. and 0.17 per cent. of blood concentration.

As we have said, one of the main objects of our study was to gain information from this neglected field. For the purpose the blood and urine were examined at frequent intervals after the administration of glucose or the injection of epinephrin in the hope that we would in a number of instances hit on the point of blood sugar concentration where sugar just begins to appear in the urine, or to disappear from it. Table 35 shows the renal threshold in the instances in which it could be estimated with reasonable accuracy. The charts show the experiments in detail and full data are given in the tables accompanying the uncharted cases.

SUMMARY

In normal persons the renal threshold is not a constant factor, but is usually above 0.17 per cent. of blood sugar concentration, and in the few instances where it could be determined accurately it lay between 0.17 per cent. and 0.18 per cent. In two instances, and we have since found two more, the renal threshold was much lower, namely, below 0.14 per cent., and these persons may have glycosuria after carbohydrate feeding even though the blood sugar curve is within the normal reaction limits. The important practical significance of this observation need scarcely be emphasized. We predict that many otherwise healthy persons with occasional glycosuria will be found on careful observation to belong to this interesting group with low renal threshold. The relation of this group to renal diabetes is also obvious. No doubt further study will disclose persons with renal thresholds varying from the normal between 0.17 per cent. and 0.18 per cent. down to 0.08 per cent. and lower. At just what level will they be classed as renal diabetics? We think it altogether likely that no definite level can be fixed and that renal diabetes will remain, as it is, a relative condition. In this connection we wish to add the chart from a patient who clinically presents unusually well the characters of renal diabetes. The case has been reported in full by Lewis and Mosenthal,¹⁷ After 100 gm. of glucose the blood sugar does not exceed 0.12 per cent., but a large amount of sugar is put out in the urine. Indeed, there is abundant glycosuria in the early morning when the fasting blood sugar is 0.84 per cent.

In nephritis the renal threshold is often above 0.20 per cent. That there is a high renal threshold in nephritis is generally known, but it is very puzzling to explain why some patients with nephritis have a high threshold and others, clinically identical, have a normal threshold. Case 18 in this series with marked hypertension and a phthalein output of 33 per cent. had a normal threshold. Recently we observed a patient with a blood pressure well over 200 mm. Hg, and a phthalein

17. Lewis and Mosenthal: *Bull. Johns Hopkins Hosp.*, 1916, **27**, 133.

output of only 15 per cent. who had a low renal threshold for glucose, namely, in the neighborhood of 0.15 per cent.

The patients observed by us with disturbed thyroid function and various other conditions had a renal threshold between 0.17 per cent. and 0.18 per cent. Case 26 with exophthalmic goiter and evidence of a mild nephritis had a slightly higher threshold, namely, between 0.19 per cent. and 0.2 per cent.

In diabetes very interesting variations are discovered. In the mild cases the renal threshold is at the normal level, but in a number of the moderately severe cases and in one of the severe the threshold was below 0.15 per cent. Our studies were made on patients who had become sugar free after treatment, and in this series we were not fortunate enough to discover any with a high threshold. However, there is abundant clinical evidence to illustrate the frequency of a high threshold in this disease. In the terminal stages it is almost the rule, and it must be emphasized that the renal impermeability is by no means constantly associated with a nephritis that is demonstrable clinically. The renal threshold for glucose is an important practical factor in the study of diabetes. It will be interesting to discover the clinical differences between the patients with low and those with high thresholds and to determine under what conditions the threshold may vary, for it may vary in the same patient.

Finally, we wish to call attention to one more important feature of our studies. It will be noted that in many instances when there is a considerable glycosuria the excretion of sugar continues long after the blood sugar has fallen below the level at which it first appeared. Charts 3, 4, 14, 17 and 28 illustrate the condition very well.

CONCLUSIONS

1. In normal persons after 100 gm. of glucose there is only a moderate hyperglycemia that rapidly subsides, the blood sugar remaining below 0.15 per cent. and again reaching the fasting level or in many instances a still lower level in from one to two hours.

2. In patients with a lowered carbohydrate tolerance, notably in diabetes, the hyperglycemia is more pronounced and more prolonged, the blood sugar usually exceeding 0.2 per cent. and the reaction lasting from three to five hours.

3. Increased carbohydrate tolerance is indicated by a subnormal reaction, the blood sugar in such instances showing only an insignificant rise.

4. As far as may be judged from the alimentary test the disturbance of glucose utilization is essentially the same in diabetes and in other conditions with low sugar tolerance, such, for instance, as is commonly found in nephritis and in deranged thyroid and hypophysial function.

5. The renal threshold for glucose in normal persons is between 0.17 per cent. and 0.18 per cent. of blood concentration.

6. The normal threshold is likewise found in many patients with lowered carbohydrate tolerance.

7. Some otherwise normal persons have a low renal threshold, that is, below 0.14 per cent. This observation has an important bearing on our conception of renal diabetes.

8. Many cases of nephritis have a high threshold, so that although the blood sugar may exceed 0.2 per cent. only a trace of sugar or none appears in the urine.

9. Mild cases of diabetes usually have a normal threshold; many severe cases have a lowered threshold. This lowered threshold may be a factor in the severity.

10. As the kidneys excrete sugar there is a tendency for the threshold to fall so that although sugar may first appear when the blood sugar reaches 0.17 per cent., sugar may still be excreted after it has dropped to 0.1 per cent.

11. A study of alimentary hyperglycemia and glycosuria as carried out in these observations gives a valuable insight into the carbohydrate economy. The test is particularly valuable to investigate patients with slight or occasional glycosuria. It decides at once whether the glycosuria is due to a metabolic disturbance, to a low renal threshold or to a combination of both factors. If the renal threshold be high it may indicate a more serious disturbance of glucose utilization than the slight glycosuria would suggest.

12. Following the subcutaneous injection of epinephrin a marked hyperglycemia occurs that reaches its maximum in one hour and then subsides as rapidly as it arose, the whole reaction occupying two hours.

13. There is no relation between the degree of alimentary hyperglycemia and the degree of epinephrin hyperglycemia.

14. When the alimentary glucose test shows certain abnormalities in the character of the blood sugar reaction these same abnormalities are reproduced in the epinephrin curve.

15. The action of epinephrin on sugar metabolism is independent of its other actions; there is no constant relation between the hyperglycemia, the vascular effects and the diuresis.

16. Epinephrin has no effect on the renal permeability for glucose.

17. Atropin diminishes the effect of epinephrin on the mobilization of sugar; pilocarpin usually increases the effect. When atropin acts in this respect as a marked depressant, pilocarpin has little or no influence; when atropin acts but slightly, pilocarpin greatly exaggerates the epinephrin effect.

OBSERVATIONS ON KIDNEY FUNCTION IN DIABETES MELLITUS *

R. FITZ, M.D.

NEW YORK

In the history of diabetes numerous theories as to the cause of the disease have been proposed, although no single one has had an anatomic basis definite enough to establish the underlying pathologic process. At present, while the etiology of diabetes is believed by most observers to be due to insufficiency of the internal secretion of the pancreas, yet pathologic anatomists have demonstrated that the kidneys of diabetic patients usually show certain well defined and characteristic lesions.

Armanni¹ was the first to point out that in diabetes there was an almost specific injury to the epithelium of the straight tubules by which they lost their cytoplasm and were transformed into hyaline-like vesicles without definite structure. Ebstein² confirmed this finding and described in coma a typical massing together of necrotic cells. Finally, Ehrlich³ proved that the peculiar hyaline degeneration described by Armanni was due to the deposition of glycogen in the cells and that the so-called "glycogenic degeneration" could be found in the majority of cases.

Albertoni and Pisenti⁴ fed rabbits and dogs with acetone, producing first albuminuria and eventually hyaline changes analogous to those already described, without, however, causing glycogenic degeneration. Trambusti and Nesti⁵ were able to produce similar lesions in phlorizinized dogs when the animals excreted appreciable amounts of acetone in the urine. Thus it has been shown by both clinical and experimental material that the diabetic kidney has a more or less definite anatomic appearance which is comparable to that obtained in animals associated with the passage of acetone bodies from the blood into the urine. In view of these findings it is interesting that no systematic studies as to the relation of the kidney function to diabetes have been recorded. Work already reported and abundantly confirmed, however, has brought out four interesting features in this respect.

* Submitted for publication May 24, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, and the Hospital of The Rockefeller Institute, New York.

1. Armanni: Quoted by Cantani, *Le diabète sucré, et son traitement diététique*, 1876.

2. Ebstein: *Deutsch. Arch. f. klin. Med.*, 1881, **28**, 143; 1882, **31**.

3. Ehrlich: *Ztschr. f. klin. Med.*, 1883, **6**, 33.

4. Albertoni and Pisenti: *Arch. f. exper. Path. u. Pharmakol.*, 1887, **23**, 393.

5. Trambusti and Nesti: *Ziegler's Beitr. z. path. Anat.*, 1893, **14**, 337.

First, the diabetic kidney is at times under the influence of a diuretic. This has been shown most simply by the characteristic symptoms of polyuria and polydipsia, and somewhat more systematically by the relation between the day and night urine. Laspeyres⁶ found a nocturnal polyuria in two out of five cases of diabetes studied, and Carles⁷ in six cases. Lépine mentions that in diabetes the normal difference between day and night urine is less marked, an observation confirmed by Péhu⁹ and Külz.¹⁰

Secondly, albuminuria either constant, intermittent or terminal, is found in many cases. Thus Aldehoff¹¹ found albuminuria in 79 per cent. of 680 observations, von Noorden¹² in 21 per cent. of 650 observations, and various other writers in from 10 to 68 per cent. of their cases. While the discrepancy in figures is wide, possibly owing to the different methods of analysis employed, yet the fact remains that the diabetic kidney is abnormally prone to albuminuria.

Thirdly, edema may occur. Naunyn¹³ says that edema is not a rare occurrence in cachetic patients with severe diabetes. Williamson¹⁴ has observed anasarca in more than 5 per cent. of his patients, Frerichs¹⁵ in twenty-five out of 400 cases, and Joslin and Goodall¹⁶ in seven cases at a time when the patients presented slight, if any, other evidence of heart or kidney disease.

Finally, the urine of patients on the verge of coma has been found repeatedly to contain masses of hyaline and granular casts, the so-called "Komazylinder" of Aldehoff.

The present paper reports studies on renal function in diabetes under varying conditions of glycosuria, hyperglycemia and acidosis. It seemed of greatest interest to study the effect on the kidney of sugar and acetone bodies because they are usually not a feature in nephritis. Moreover, it is generally believed that an increasing concentration of sugar in the blood without concomitant glycosuria is due to a specific holding back of sugar on the part of the diabetic kidney, a fact which in itself is evidence of abnormal kidney function. Under normal conditions, too, the organism depends on the kidney to regulate the acid-base equilibrium. Unless the rate of elimination of acids keeps up

6. Laspeyres: *Deutsch. Arch. f. klin. Med.*, 1900, **68**, 192.

7. Carles: *Province méd.*, 1906.

8. Lépine: *Le diabète sucré*, 1909.

9. Péhu: *Revue de méd.*, 1903, p. 279.

10. Külz: *Klinische Erfahrungen über Diabetes mellitus*, 1899.

11. Aldehoff: Quoted from Külz, Footnote 10.

12. Von Noorden: *Die Zuckerkrankheit und ihre Behandlung*, 1912.

13. Naunyn: *Diabetes Mellitus*, 1906.

14. Williamson: *Diabetes Mellitus and Its Treatment*, 1898, p. 227.

15. Frerichs: *Ueber den Diabetes*, 1884.

16. Joslin and Goodall: *Experiments on an Ash-Free Diet and Salt Metabolism*, *Jour. Am. Med. Assn.*, 1908, **51**, 727.

with their rate of production, true "acidosis" results. Thus the permeability of the kidney for both sugar and acid may well be an important factor in helping to establish the symptoms due to glycosuria and acidosis.

At present, the common tests for renal function used in heart and kidney diseases in addition to urinalysis are the phenolsulphone-phthalein test of Rowntree and Geraghty,¹⁷ some form of "test renal meal" as advocated by von Monakow,¹⁸ Hedinger and Schlayer,¹⁹ O'Hare,²⁰ and Mosenthal,²¹ estimation of nonprotein nitrogen or urea of the blood alone as advocated by Ascoli,²² Strauss,²³ and Folin,²⁴ or in relation to the simultaneous excretion of urea in the urine according to the method of Ambard²⁵ and McLean,²⁶ and estimation of the blood chlorid in relation to its excretion in the urine according to Ambard's laws. Comparative studies with those tests in nephritis have shown that as the renal function becomes impaired, the excretion of phenolsulphonephthalein diminishes, the nonprotein nitrogen and urea of the blood increase, the kidney is less able to excrete nitrogen and in certain instances water and sodium chlorid, and the ratio between urea in the blood and that in the urine changes so that Ambard's constant for urea becomes higher as McLean's index becomes proportionally lowered. Interesting information in regard to renal physiology has been obtained by such tests and two significant conclusions have been drawn: (1) Ambard and McLean have demonstrated that the excretion of certain substances from the blood through the kidney into the urine is carried on according to laws capable of numerical expression. (2) The kidney has selective and independent powers of excretion for several of the different urinary constituents.

For the studies reported here a series of cases of diabetes of differing severity was selected. Renal function in relation to the excretion of urea and sodium chlorid was tested by McLean's adaptation of the Ambard constant. These tests seemed sufficiently comprehensive

17. Rowntree and Geraghty: *Jour. Pharm. and Exper. Therap.*, 1909, **1**, 579.

18. Von Monakow: *Deutsch. Arch. f. klin. Med.*, 1911, **102**, 248.

19. Hedinger and Schlayer: *Deutsch. Arch. f. klin. Med.*, 1914, **114**, 120.

20. O'Hare: *A Study of Salt, Nitrogen and Water Excretion in Nephritis*, THE ARCHIVES INT. MED., 1916, **17**, 711.

21. Mosenthal: *Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine*, THE ARCHIVES INT. MED., 1915, **16**, 733.

22. Ascoli: *Arch. f. d. ges. Physiol.*, 1901, **87**, 103.

23. Strauss: *Die Chronische Nierentzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung*, 1902.

24. Folin and Denis: *Jour. Biol. Chem.*, 1912, **11**, 527.

25. Ambard: *Physiologie Normale et Pathologique des Reins*, 1914.

26. McLean: *Clinical Determination of Renal Function by an Index of Urea Excretion*, *Jour. Exper. Med.*, 1915, **22**, 212, 336; *Jour. Am. Med. Assn.*, 1916, **66**, 415.

because McLean has shown that the urea index is a good indicator of total renal function, gives practically the same information as the phenolsulphonephthalein test, and is preferable to those tests which rely on blood analysis alone, since they can be interpreted only when the intake of the substance studied is known. The chlorid excretion was determined in addition, to study renal function in more than one way. "Test meal" studies were not made because the cases differed so widely in severity as to make a common diet for all impossible. The blood and urine sugar, as well as the carbon dioxid tension of the alveolar air,²⁷ were estimated to disclose any relation between abnormal renal function, as illustrated by ordinary tests, and glycosuria or abnormal amounts of sugar or acetone bodies in the blood. Obviously, the carbon dioxid tension of the alveolar air gave an indirect measure of the blood acetone bodies. Winterstein²⁸ and Hasselbalch,²⁹ however, have established that variations in the carbon dioxid content of the blood, and consequently of the alveolar air, are inverse to the production of nonvolatile acids. Observations to be published in another paper show that in diabetes the fall in the alveolar carbon dioxid which occurs in acidosis is more or less parallel to the increase of acetone bodies in the blood; thus the information so obtained was significant.

The tests were all made in the same fashion according to McLean's adaptation of Ambard's methods. The patients were taken for observation in the morning before breakfast to avoid the effect of feeding. One-half hour before the period began the subjects were given 150 or 200 c.c. of water and took no more fluid or food until the observation period was ended. At the beginning of the period the bladder was emptied. Thirty minutes later about 25 c.c. of blood was taken from an arm vein into a dry tube containing about 100 mg. of powdered potassium oxalate to prevent clotting. At the same time samples of alveolar air were obtained. At the end of 72 minutes³⁰ after the bladder was first emptied, the specimen of urine secreted during the 72-minute period was collected, carefully measured and used for analysis.

27. The carbon dioxid tension of the alveolar air was determined in the Peter Bent Brigham Hospital cases. In the others it was calculated from the capacity of the blood plasma to combine with carbon dioxid (Van Slyke: Jour. Biol. Chem., 1917, **30**, 289), the volume per cent. of carbon dioxid bound by the plasma being multiplied by 0.69 in order to make the results numerically comparable to alveolar carbon dioxid tensions expressed in millimeters of mercury. The results from the two methods are usually alike, as has been shown by Van Slyke and by Frothingham and Walker (*THE ARCHIVES INT. MED.*, 1916, **18**, 304), although in diabetes the alveolar air sometimes indicates acidosis when the blood alkali is really normal (Stillman, Van Slyke, Cullen and Fitz: Jour. Biol. Chem., 1917, **31**, 405).

28. Winterstein: Arch. f. d. ges. Physiol., 1911, **138**, 167.

29. Hasselbalch: Biochem. Ztschr., 1912, **46**, 403.

30. In a few cases the length of time was one or two hours. In such instances the blood was drawn in the middle of the time selected.

A 72-minute period was ordinarily taken, since it is one-twentieth of 24 hours, and the calculation of the rate of excretion for 24 hours was made simple.

A portion of the blood was analyzed for urea by the method of Van Slyke and Cullen,³¹ and for sugar by the Benedict-Lewis³² method, except in a few cases when Bang's³³ micromethod was used. The remainder of the blood was centrifugalized and the plasma pipetted off. A portion of the plasma was analyzed for sodium chlorid by the McLean and Van Slyke³⁴ method, and for the combining power for carbon dioxid according to Van Slyke's³⁵ method. Alveolar air samples were collected according to the Plesch³⁶ method and were analyzed in a Haldane³⁷ gas analysis instrument. Since the blood or air was taken in about the middle of the period, it was assumed to represent the concentration in the blood for the substances whose simultaneous excretion in the urine was studied. The urine was analyzed for sugar by Benedict's³⁸ method or polarization in a few instances; for chlorids by a modified Volhard titration; and for urea and ammonia by Van Slyke and Cullen's method. The results are divided into two groups dealing with (1) the urea index, and (2) the relation of plasma chlorid to the excretion of chlorid in the urine.

In Table 1 are recorded observations on the urea index. In considering the results it is necessary to compare them with similar observations on normal individuals. McLean has published 107 such tests made according to the same methods, which serve as a good control. His tables show that the normal concentration of urea in the blood varies from 0.2 to 0.5 gm. per liter. The normal urea index varies between 80 and 200, with an average reading of 120 based on 100 tests. Any index below 80 is considered abnormal, and the degree of impairment of functional ability or damage to the kidneys becomes greater as the index gets lower. Any index above 200 is abnormal, although its significance is less certain. A high index may occur in healthy young individuals with low blood urea; it may result from the washing out of urea with a high fluid output; or it may occur with "vascular hypersensitiveness," according to the conception of Schlayer. Repeated indexes made on the same normal individual at different times may

31. Van Slyke and Cullen: *Jour. Biol. Chem.*, 1914, **19**, 211.

32. Benedict and Lewis: *Jour. Biol. Chem.*, 1915, **20**, 61.

33. Bang: *Der Blutzucker*, 1913.

34. McLean and Van Slyke: *Jour. Biol. Chem.*, 1915, **21**, 361.

35. Van Slyke: *Jour. Biol. Chem.*, 1917, **30**, 289.

36. Plesch: *Ztschr. f. exper. Path. u. Therap.*, 1909, **3**, 380.

37. Haldane: *Methods of Gas Analysis*, 1912.

38. Benedict: The Detection and Estimation of Glucose in Urine, *Jour. Am. Med. Assn.*, 1911, **57**, 1193.

TABLE 1.—THE RELATION OF THE RATE OF UREA EXCRETION TO CONCENTRATION IN BLOOD ARRANGED ACCORDING TO THE UREA INDEX

$$\text{Index (I)} = \frac{\text{Gm. per 24 hrs.} \sqrt{\text{Gm. per liter}} \times 8.96}{\text{Wt. in Kg.} \times (\text{Blood Urea})^2}$$

Number	Subject	Weight, Kg.	24 Hour Urine, O.c.	Urea			Index I
				Gm. per Liter of Blood Ur	Gm. per Liter of Urine O	Gm. per 24 Hrs. D	
1	P. B. B. H. 6353	30.0	3,600	0.726	6.99	25.20	37
2	P. B. B. H. 6493	70.6	3,072	0.453	9.09	27.92	50
3	R. I. H. 2341	54.0	1,694	0.167	3.72	6.30	72
4	Fl.	45.0	6,000	0.360	4.16	25.00	79
5	R. I. H. 2234	50.0	2,000	0.410	12.35	24.70	93
6	R. I. H. 2480	47.0	1,680	0.273	8.11	13.62	100
7	P. B. B. H. 5921	61.7	2,880	0.267	6.76	19.47	104
8	R. I. H. 2128	40.2	1,500	0.314	10.05	15.10	108
9	P. B. B. H. 5938	40.0	4,800	0.280	3.94	18.91	108
10	P. B. B. H. 6328	68.3	1,200	0.494	30.77	36.92	110
11	P. B. B. H. 5975	64.0	1,080	0.377	25.66	27.71	138
12	P. B. B. H. 6364	64.2	1,560	0.265	12.60	19.66	139
13	R. I. H. 2280	28.5	800	0.232	9.64	7.70	140
14	P. B. B. H. 6032	48.0	1,440	0.257	10.75	15.48	144
15	R. I. H. 2680	48.0	2,000	0.262	8.88	17.76	144
16	R. I. H. 2525	47.8	4,080	0.190	3.60	14.70	145
17	L. T.	50.0	2,540	0.260	8.09	20.58	156
18	R. I. H. 2111	49.2	5,400	0.225	4.07	22.00	160
19	R. I. H. 2684	31.7	6,740	0.169	1.81	12.20	162
20	P. B. B. H. 6483	61.9	1,200	0.272	17.61	21.13	174
21	O. R.	37.3	3,460	0.162	3.11	10.75	175
22	R. I. H. 2382	46.5	1,740	0.220	9.16	15.94	192
23	P. B. B. H. 6205	62.0	780	0.212	18.23	14.22	198
24	R. I. H. 2516	87.2	2,997	0.307	15.40	46.13	198
25	R. I. H. 2414	39.8	1,280	0.165	7.11	9.09	200
26	M. L.	64.0	3,840	0.218	6.98	26.40	205
27	R. I. H. 2394	42.0	2,800	0.215	6.37	17.70	206
28	P. B. B. H. 5564	52.0	3,360	0.135	3.51	11.79	210
29*	Fl.	95.4	6,000	0.230	7.44	44.64	217
30	Di.	48.7	2,200	0.192	7.38	16.24	220
31	R. I. H. 2487	50.2	1,800	0.092	3.26	5.86	223
32	R. I. H. 2469	50.4	5,000	0.160	4.17	20.85	296
33	O. A.	60.0	2,900	0.222	10.60	30.74	305
34	R. I. H. 2686	25.8	2,700	0.109	2.52	6.80	315
35	P. B. B. H. 5593	65.6	1,500	0.210	16.71	25.06	320
36	R. I. H. 2457	52.2	3,500	0.152	7.62	26.67	550
37	R. I. H. 2679	41.2	3,400	0.115	5.06	17.20	635
38*	P. B. B. H. 6482	71.3	7,320	0.240	20.65	151.16	1498

* Excluded from table of averages.

show such marked differences as from 87 to 196. The meaning of such variation is not defined.

Table 1 shows that twenty-one cases of diabetes, or 56 per cent. of those studied, have a urea index within normal limits. Thirteen cases, or 34 per cent., have an index above 200; four cases, or 10 per cent., have an index below 80, and must therefore be considered to have an impaired renal function. It is of interest that such a large number of cases should have a high index, especially when it is realized that the average index of those cases within normal limits is 146, which is significantly higher than McLean's normal average of 120. One reason for such findings may be the low blood urea found in several cases. Thus Case 31, with an index of 223, had a blood urea of 0.092 gm. per liter, Case 25 an index of 200, with 0.165 gm. of urea per liter of blood, and Case 28 an index of 210, with 0.135 gm. of urea per liter of blood. A more probable explanation lies in the high fluid output which occurred frequently. For instance, in the thirteen cases with an index above 200, the rate of water excretion for twenty-four hours was never below 1,500 c.c., in one case it reached 7,320 c.c., and averaged 3,770 c.c., while in the entire series the lowest output was 780 c.c. per twenty-four hours, and the average was 3,034 c.c. In McLean's normals, on the other hand, the highest fluid output encountered was 5,400 c.c., the lowest was 462 c.c., while the average was 1,738 c.c.

The patients, both normal and diabetic, had taken the same amount of fluid to drink at the same time before the period was begun. It therefore seemed that the diabetic kidney often had a rate of water elimination more rapid than normal. Since acids or sugar might possibly produce such a diuretic effect, the rate of water excretion per twenty-four hours was compared with the height of blood sugar, with the glycosuria, and with the degree of acidosis in those cases with a normal or high urea index. The results of this study are shown in Table 2.

The results studied from this point of view are inconclusive. Of the thirty-four observations, twenty-three had a fluid output above the average normal rate of 1,740 c.c. in twenty-four hours. In this group acidosis could not be assumed to produce the polyuria, as cases with a low alveolar air showed no tendency to excrete more fluid than did those with high alveolar air. Twelve cases showed an appreciable excretion of sugar. The fluid output in these cases bore relation neither to the total excretion in twenty-four hours nor to the concentration of sugar per liter of urine. The sugar-free cases appeared to excrete water with as much ease as those with glycosuria. It is of possible significance that only four of the twenty-three cases had a blood sugar below 0.17 per cent. This observation alone might suggest that hyper-

TABLE 2.—THE RELATION OF THE RATE OF WATER EXCRETION IN TWENTY-FOUR HOURS TO SUGAR EXCRETION, AND TO CONCENTRATION IN THE BLOOD OF SUGAR OR ACIDS (AS ESTIMATED BY THE CARBON DIOXID TENSION OF THE ALVEOLAR AIR) IN THOSE CASES OF DIABETES WITH A UREA INDEX ABOVE 80. TABULATED ACCORDING TO THE FLUID OUTPUT

Number	Subject	Weight, Kg.	24-Hour Urine, C.c.	Sugar			Alveolar CO ₂ , Mm.
				Gm. per Liter of Blood S	Gm. per Liter of Urine C	Gm. per 24 Hrs. D	
1	P. B. B. H. 6482	71.3	7,320	3.40	18.50	135.42	39.9
2	R. I. H. 2684	31.7	6,740	1.37	Negative	42.6
3	Fl.	95.4	6,000	2.26	7.50	45.00	35.0
4	R. I. H. 2111	49.2	5,400	2.00	Traces	37.8
5	R. I. H. 2469	50.4	5,000	1.33	Negative	38.9
6	P. B. B. H. 5938	40.0	4,800	3.18	12.50	60.00	12.8
7	R. I. H. 2525	47.8	4,080	1.56	Negative	40.2
8	P. B. B. H.	64.0	3,840	1.49	Negative	40.8
9	R. I. H. 2457	52.2	3,500	2.94	18.52	64.82	23.2
10	C. R.	37.3	3,460	2.63	32.30	111.50	15.5
11	R. I. H. 2679	41.2	3,400	2.86	Negative	43.2
12	P. B. B. H. 5564	52.0	3,360	2.30	Negative	37.3
13	R. I. H. 2516	37.2	2,997	2.63	16.40	49.14	38.8
14	P. B. B. H. 5921	61.7	2,880	2.16	Traces	31.6
15	R. I. H. 2394	42.0	2,800	2.33	22.20	62.00	20.2
16	C. A.	60.0	2,900	2.50	23.80	69.02	35.0
17	R. I. H. 2686	25.8	2,700	2.00	Negative	41.3
18	L. T.	50.0	2,540	2.56	41.60	106.00	29.6
19	Di.	48.7	2,200	4.35	34.48	75.85	36.8
20	R. I. H. 2650	48.0	2,000	3.00	16.00	32.00	20.1
21	R. I. H. 2234	50.0	2,000	2.08	Negative	38.2
22	R. I. H. 2487	50.2	1,800	2.38	Negative	42.2
23	R. I. H. 2382	46.5	1,740	3.12	23.20	40.37	35.3
24	R. I. H. 2480	47.0	1,680	4.16	Traces	33.0
25	P. B. B. H. 6364	64.2	1,560	1.37	Negative	38.2
26	P. B. B. H. 5593	65.6	1,500	1.72	Negative	42.5
27	R. I. H. 2123	40.2	1,500	2.08	Negative	36.2
28	P. B. B. H. 6032	48.0	1,440	1.03	Negative	39.1
29	R. I. H. 2414	39.8	1,280	1.67	Negative	47.6
30	P. B. B. H. 6483	61.9	1,200	2.92	31.00	37.20	33.9
31	P. B. B. H. 6328	68.3	1,200	2.56	22.00	26.40	35.1
32	P. B. B. H. 5975	64.0	1,080	1.43	Negative	38.7
33	R. I. H. 2280	28.5	800	3.12	Negative	36.9
34	P. B. B. H. 6205	62.0	780	2.82	Negative	32.5

glycemia was an important factor in diuresis. But against this are the eleven cases with a more nearly normal fluid output, five of which had a hyperglycemia well above 0.17 per cent.

On the whole, it appears from this series of cases that many diabetics have an abnormally high urea index. This is probably due in part to a washing out of urea through an increased output of fluid. Such polyuria does not depend on acidosis or glycosuria, but is apt to be coincident with a pronounced hyperglycemia. These findings suggest that the diabetic kidney is ordinarily hyperfunctional and hypersensitive to such a diuretic as an increased amount of sugar in the blood. They may explain in a measure the observations of earlier workers who commented on the frequency of nocturnal polyuria in the disease.

Of much greater interest both from the point of view of kidney function and diabetes are those cases with a urea index below 80, or, in other words, those cases with a definitely impaired renal function. These cases will be discussed in detail and will include certain other cases which should be placed in the same group for comparison. The cases fall into two divisions, the first consisting of one case in which the abnormal renal function was probably due to a coexistent chronic nephritis, and the second including seven cases of impending or true diabetic coma.

REPORT OF CASES

The first case, R. I. H. 2341, was a Russian woman aged 51. During a pregnancy twenty-eight years previously, the patient apparently had an attack of acute nephritis which recurred a year before entry to the hospital. Her diabetic symptoms were of two and one-half years' duration. Her physical examination was essentially negative except for an enlarged heart with an apical systolic murmur, and a blood pressure which on repeated examinations was above 190 systolic. The urine had a large trace of albumin and was without casts in the sediment. In view of the patient's history and physical examination it seemed probable that the urea index of 72 was due to a chronic nephritis, and was independent of her diabetes, which was relatively mild.

Of the coma cases, the first, C. R., was a young woman 30 years old. Her diabetes was of three years' duration, had shown a progressive, downward tendency and was accompanied by great emaciation and weakness. When seen, her physical examination was negative. Mentally she was bright and said that she was no more uncomfortable than she had been for a year. Her breathing, however, was abnormally deep, and her pulse was small and rapid. The carbon dioxide tension of her alveolar air was 15.5 mm. The urine contained acetone, diacetic acid and much sugar. There was a large trace of albumin and the sediment contained many hyaline and granular casts. Renal function tests showed a urea index of 280. The patient was treated by her own physician who reported her death about ten days later.

Three cases were seen at shorter intervals before death.

F1. was a Russian aged 60 years, with diabetes of several years' duration. A month previously he developed a carbuncle on his neck, which was still draining, though apparently in good condition. Two days before being seen he became alarmingly sleepy and short of breath. When seen, he still could be

roused, though he was evidently in a serious condition. His physical examination was negative except for his carbuncle and a diffuse bronchitis. His pulse was rapid and weak. His breathing showed marked air hunger. The urine contained much acetone, diacetic acid and sugar, had a heavy trace of albumin, and was loaded with hyaline and granular casts. Here again the carbon dioxid tension of the alveolar air was low (23.2 mm.). The urea index was 79. The patient continued to grow worse and died in a few days. No further studies on renal function could be made.

The third case, P. B. B. H. 6353, was that of a boy aged 13 years, with symptoms of diabetes of a few months' duration. The day before entry he suddenly became dyspneic and went into deep coma. His urine in addition to acetone, diacetic acid and sugar, contained a large trace of albumin and had showers of hyaline and granular casts in the sediment. The renal function tests showed a urea index of 36.5, pointing to a severe injury to his kidneys. Associated with this was a carbon dioxid tension in the alveolar air of 12.8 mm. The patient died in a few hours.

The fourth case, R. I. H. 2787, was a girl aged 12 years. Her diabetes was of a year's duration. She first entered the hospital Nov. 16, 1916, with considerable acidosis and glycosuria which cleared up under treatment. At the time of entry her urine contained albumin and casts, her urea index was 510, her glycosuria was 27 gm. to the liter or 89 gm. in twenty-four hours, and her blood sugar was 0.31 per cent. Her alveolar carbon dioxid tension was 23.3 mm. She was discharged Dec. 23, 1916, in good condition.

She reentered March 10, 1917, in coma. According to the history she had been well until the day before, when she began to feel "short of breath" and subsequently had grown stuporous. She died in a few hours after reaching the hospital. Her urine on this admission contained more albumin than on the time before, but fewer casts. Her urea index was 34, her glycosuria was 9.52 gm. to the liter or 33.74 gm. in twenty-four hours, and her blood sugar was 0.46 per cent. Her alveolar carbon dioxid tension was 10 mm.

If these four cases are grouped together as one, it is seen that as coma developed the renal function grew worse. This was best shown by the rapidly falling urea index. It so happened, moreover, that in each case the concentration and total output of sugar were comparable, yet the blood sugar increased as the urea index fell, an observation suggesting that the kidney was becoming impermeable to sugar as well as urea.

Opportunity to inquire more specifically into kidney function in diabetic coma was afforded by three other cases which were studied for several successive days.

P. B. B. H. 6493, was a woman aged 60 years. Her history was unimportant except for a characteristic diabetic history of ten years' duration. Until a week before entry into the hospital she had been reasonably comfortable. Then for no apparent reason she had become worse and on the day of entry was nearly comatose.

She was a very plethoric, obese woman. Her physical examination was negative except as to urine and blood analyses. She lived five days. By way of treatment she was fasted and was given fluids, soup, whisky and sodium bicarbonate in large doses. The progress of her illness and its effect on renal function is shown in Table 3.

At entry the urine contained albumin and casts in addition to sugar, acetone and diacetic acid. It was evident from these signs, as well as on account of such a low carbon dioxid tension of the alveolar air (23.7 mm. tension) that she had a marked acidosis. Clinically, during the three days following admis-

sion she appeared to improve. Her kidney function, however, grew worse despite the fact that enough alkali must have been absorbed to neutralize her acidosis in part and to cause a definite rise in the carbon dioxide tension of her alveolar air. On the morning of the fifth day the urea index was only 6. Her condition was so bad that it was impossible to obtain a specimen of alveolar air for analysis. She died within a few hours.

TABLE 3.—CASE P. B. B. H., 6493

Date	Wt., Kg.	24 Hr. Urine	Urea			Index	Sugar			Alveolar CO ₂ , Mm.
			Gm. per Liter Blood Ur	Gm. per Liter Urine O	Gm. per 24 Hrs. D		Gm. per Liter Urine O	Gm. per 24 Hrs. D	Gm. per Liter Blood B	
8/29/15	70.6	3,072	0.458	9.09	27.92	50	51.5	158.2	5.65	23.7
8/30/15	71.5	2,960	0.458	7.88	23.32	39	17.0	50.3	5.60	17.1
8/31/15	71.5	3,840	0.304	4.22	16.21	45	9.20	35.0	5.60	24.7
9/ 1/15	69.8	2,880	0.314	3.97	11.43	30	7.00	20.0	4.55	38.6
9/ 2/15	69.8	2,240	0.466	2.74	6.22	6	10.00	22.4	6.80	Not obtained

The excretion of sugar in this case is noteworthy. At entry the blood sugar was high and was accompanied by a relatively high sugar output. Under fasting the blood sugar showed a slight diminution, with a sudden rise taking place just before death. The sugar excretion on the other hand showed a persistent decrease.

P. B. B. H. 5938 is a similar case. The patient was a young woman aged 30 with an unimportant history except for diabetes. This was of two years' duration and had caused marked loss of weight and emaciation. The day before entry to the hospital she had become dyspneic and stupid. At entry she could still be roused but had pronounced air hunger. Her physical examination was negative except for her blood and urine. She died three days after

TABLE 4.—CASE P. B. B. H., 5938

Date	Wt., Kg.	24 Hr. Urine	Urea			Index	Sugar			Alveolar CO ₂ , Mm.
			Gm. per Liter Blood Ur	Gm. per Liter Urine O	Gm. per 24 Hrs. D		Gm. per Liter Urine O	Gm. per 24 Hrs. D	Gm. per Liter Blood S	
6/30/15	40.0	4,800	0.280	3.94	18.91	108	12.50	60.00	3.18	17.9
7/ 1/15	40.0	4,880	0.355	4.00	17.52	62	13.00	57.00	3.72	19.5
7/ 2/15	40.0	4,016	0.374	2.50	10.00	25	23.00	92.00	5.35	12.8

entry. Her treatment in the hospital consisted in whisky and fluids by mouth. In addition she was given infusions of sodium bicarbonate and glucose. Tests for renal function gave results shown in Table 4.

In this case, as well, the urea index showed a rapidly progressing drop, which may have been hastened by the fact that the acidosis was not appreciably influenced by the alkali. The blood sugar rose but interpretation of the findings in respect to it are obscured because the patient had received glucose.

R. I. H. No. 2770, was a boy aged 9 years. His diabetes was of two years' duration. On Oct. 28, 1916, he was in fairly good condition though the urine showed some sugar and a moderate ferric chlorid reaction. He entered the hospital two days later on the verge of coma. He lived for eight days, during which time he was practically comatose. At first he was fasted and given sodium bicarbonate by mouth. On the seventh day he was given two eggs and 5 gm. of carbohydrate in vegetables. Tests for renal function are given in Table 5.

TABLE 5.—TESTS FO

Date	Weight, Kg.	Urine per 24 Hrs., O.e.	Urea			Index I	Sugar		
			Gm. per Liter of Blood Ur	Gm. per Liter of Urine O.	Gm. per 24 Hrs. D		Gm. per Liter of Blood S	Gm. per Liter of Urine O	Gm. per 24 Hr. D
10/31/16	14.6	535	0.332	4.20	2.25	26.0	4.55	4.00	2.14
11/ 1/16	14.4	1,200	0.763	2.79	3.35	4.3	2.64	1.85	2.22
11/ 2/16	14.0	1,200	1.01	5.13	6.16	3.3	4.20	4.55	5.47
11/ 3/16	13.8	1,000	0.715	5.00	5.00	14.4	4.11	5.89	5.89
11/ 4/16	13.3	1,500	0.630	4.61	7.91	29.0	5.56	6.25	9.39
11/ 6/16	13.1	1,400	0.487	3.22	4.50	29.0	5.56	3.65	5.11
11/ 7/16	12.7	800	0.730	4.34	3.46	9.6	5.00	9.09	7.26

* Acetone bodies in blood and urine determined by Van Slyke's method.

In this case the urea index fell at first from 26 to 3 and then rose slightly. On the day before death it fell again. The blood sugar remained high with a comparatively small excretion of sugar in the urine. The alveolar carbon dioxide tension was low at first but rose, probably as the result of sodium bicarbonate. When the sodium bicarbonate was omitted it fell again, but returned toward normal with food. The day before death it was 33.4 mm., which would justify the conclusion that acidosis alone was not sufficient to be fatal.

Unfortunately acetone determinations were not made in the other cases. In this, however, the findings are noteworthy. The blood acetone rose to tremendously high figures while sodium bicarbonate was being given, and diminished in the blood when the drug was omitted and food was taken. On the other hand, the urinary excretion of acetone in no way kept pace with the blood concentration.

It is interesting to contrast these results with two severe cases which improved immediately under treatment and on which repeated tests were made.

R. I. H. 2680 was a woman aged 28 years with a history of diabetes developing four months before entry to the hospital. A week before, she had noticed increasing polyuria and polydipsia accompanied by dyspnea on slight exertion. Her physical examination was negative except for slight air hunger. Her urine at entry contained a trace of albumin, without casts in the sediment. There was much sugar, and a heavy diacetic acid reaction. While under observation she was fasted until she became sugar-free and was then given a diet sufficiently low in protein carbohydrate and fat to keep her urine free from sugar.

R. I. H. 2475 was a boy aged 26 months. He had been a healthy child until three weeks before entry. Then there had been a gradual onset of polyuria, polydipsia, and polyphagia. At entry the child was drowsy and extremely irritable. His physical examination was essentially negative. He was treated by fasting, after feeding for one day, and was then given carbohydrates in green vegetables to his point of tolerance. The renal function tests on the two cases are grouped together.

—RENAL FUNCTION

Acetone Bodies (including Beta-hydroxybutyric Acid)*			Alveolar O ₂ , Mm.	Urinary Findings	Remarks
Mg. per 100 C.c. of Blood A	Gm. per Liter of Urine O	Gm. per per 24 Hrs. D			
150.0	8.00	4.26	15.3	Albumin and casts	259 sodium bicarbonate
240.0	7.91	9.50	20.2	Albumin and casts	69 sodium bicarbonate
260.0	7.76	9.32	30.3	Albumin and casts	159 sodium bicarbonate
270.0	7.20	7.20	34.7	Albumin and casts	29 sodium bicarbonate
368.0	4.54	6.80	26.8	Albumin and casts	
212.0	3.84	5.38	26.9	Albumin and casts	Fast broken
192.0	2.18	1.74	33.4	Albumin and casts	Fast broken

In both cases the urea index showed considerable variation from day to day without any progressive downward tendency. Other non-fatal cases which have been followed in similar fashion have shown variation in the urea index which, however, has usually remained well above normal. Occasional cases have been encountered which have shown temporary impairment of function. Some of these have been complicated by edema and one will be described in detail later.

These cases as a whole demonstrate two significant facts: Judged by the urea index, kidney function in diabetes is usually normal. In diabetic coma, on the other hand, pronounced renal insufficiency occurs. This is shown by a falling index which tends to become progressively lower as the severity of the condition increases. Such functional derangement may be accompanied by an increase in the blood sugar, with a lessened output, suggesting that other functions beside that of urea excretion are involved. At present the underlying cause of this complication is uncertain.

McLean has confirmed Ambard and Weill as to the laws of chlorid excretion in relation to its blood concentration and has tabulated seventy-two observations on normal individuals made according to the methods used in the present paper. McLean has found that normally the plasma chlorid varies between 5.62 and 6.25 gm. per liter according to the amount of salt ingested. There is a close agreement between

the chlorid calculated in the plasma by Ambard and Weill's constants and that actually found. The maximum differences in normal individuals were, with one exception, between 0.22 above the calculated value and 0.16 below. In one case the actual chlorid was 0.38 lower than the theoretical. Under pathologic conditions relatively increased concentration of chlorid occurs in certain types of cardiac and renal disease and usually accompanies edema. Relatively low concentration of chlorid occurs in fevers and under the influence of diuretics. There is no connection between urea and chlorid functions.

As can be seen from the table, in the twenty-eight cases of this series which were studied, the plasma chlorid varied between 5.05 and 6.31 gm. per liter. In eight cases the actual plasma chlorid was higher

TABLE 6.—CASE R. I. H., 2680

Date	Weight, Kg.	24 Hr. Urine	Urea, Gm. per Liter Blood Ur	Index of Ex- cretion I	Sugar			Alveo- lar CO ₂ , Mm.
					Gm. per Liter Blood S	Gm. per Liter Urine C	Gm. per 24 Hrs. D	
10/16/15	48.0	2,000	0.262	144	3.00	16.00	32.00	20.1
10/17/15	48.4	2,000	0.180	230	2.70	14.30	28.60	28.7
10/18/15	49.5	6,800	0.150	142	2.62	3.00	20.40	41.4
10/20/15	49.4	2,680	0.162	210	2.33	3.77	10.10	39.5
11/3/15	11.8	1,020	0.336	414	5.70	43.48	44.35	21.8
11/4/15	11.8	1,680	0.408	256	4.65	32.26	54.20	23.6
11/5/15	11.7	600	0.186	227	2.00	3.70	2.22	27.8
11/6/15	12.2	2,300	0.228	310	1.44	Traces	Traces	23.6
11/8/15	12.2	800	0.262	230	1.54	Negative	Negative	29.4

than the calculated, while in the remaining twenty it was lower. This confirms McLean, who found a similar lowering of the plasma chlorid in the majority of his observations on twenty-eight other cases of diabetes. By comparing the rate of chlorid excretion with the degree of acidosis, the urea index and the blood sugar, no interrelationship could be found. It would seem that in diabetes as well as nephritis the modes of excretion of urea and chlorid are independent.

Studies were made in three cases which may throw light on edema in diabetes.

R. I. H. 2394, was a man aged 31 years. He entered the hospital in March, 1915, with diabetes of short duration. His glycosuria responded to fasting and he was discharged sugar-free on a fairly liberal mixed diet. During his first stay in the hospital his urine was albumin-free and did not contain casts. For six months after discharge he did well. Then he grew careless, ate a

TABLE 7.—THE RELATION OF THE RATE OF CHLORID EXCRETION (CALCULATED AS SODIUM CHLORID) TO CONCENTRATION IN PLASMA.
ARRANGED ACCORDING TO RATE OF EXCRETION AS MODIFIED BY CONCENTRATION IN URINE AND EXPRESSED AS

Calculated plasma NaCl = $5.62 + \sqrt{\frac{\text{Gm. per 24 hrs. } \sqrt{\text{Gm. per liter}}}{\text{Wt. in Kg.} \times 4.23}}$

Number	Subject	Weight, Kg.	24 Hrs. Urine, C.c.	Blood Urea per Liter	Index of Urea Excretion	Blood Sugar per Liter	Alveolar CO ₂ , Mm.	Sodium Chlorid			
								Gm. per 24 Hrs. D	Gm. per Liter of Plasma	Calculated	Actual
1	P. B. B. H.	40.0	4,800	0.280	108	3.18	17.9	0.96	5.67	5.56	-0.11
2	P. B. B. H.	70.6	3,072	0.158	50	5.65	23.7	1.87	5.69	5.03	-0.66
3	P. B. B. H.	65.6	1,500	0.210	320	1.72	12.5	2.55	5.73	6.35	+0.62
4	P. B. B. H.	39.0	3,000	0.136	36	4.35	12.8	2.15	5.73	6.23	+0.50
5	P. B. B. H.	48.0	2,000	0.362	144	3.00	20.1	3.40	5.77	6.01	+0.24
6	R. I. H.	61.7	2,880	0.267	101	2.16	31.6	6.31	5.81	6.22	+0.41
7	P. B. B. H.	64.0	1,050	0.377	183	1.43	38.7	5.51	5.83	6.31	+0.48
8	P. B. B. H.	62.4	1,410	0.212	232	2.05	11.9	4.70	5.86	5.60	-0.26
9	P. B. B. H.	54.0	1,694	0.167	72	1.25	11.0	7.15	5.88	5.87	-0.01
10	R. I. H.	1,570	1,570	0.265	189	1.37	38.2	7.06	5.88	5.87	-0.01
11	P. B. B. H.	32.3	3,860	0.135	210	2.30	37.3	9.07	5.83	6.02	+0.19
12	P. B. B. H.	42.0	2,500	0.215	293	2.33	20.2	7.70	5.89	5.67	-0.22
13	R. I. H.	52.2	3,500	0.152	350	2.14	23.2	10.15	5.90	5.26	-0.64
14	R. I. H.	53.8	1,280	0.165	270	1.67	17.6	6.52	5.92	5.33	-0.59
15	R. I. H.	60.0	2,000	0.222	307	2.50	35.0	12.18	5.93	5.31	-0.62
16	G. A.	70.0	2,210	81	1.10	33.1	12.32	5.93	6.03	+0.10
17	R. I. H.	25.8	2,700	0.109	315	2.00	11.3	7.07	5.96	5.76	-0.20
18	R. I. H.	50.0	2,000	0.110	93	2.03	18.2	11.50	5.93	5.33	-0.60
19	L. T.	50.0	2,540	0.170	156	2.46	20.6	14.20	6.02	5.26	-0.76
20	R. I. H.	87.2	2,997	0.207	198	2.63	28.8	21.37	6.01	6.09	+0.08
21	Di.	31.7	2,000	0.192	250	1.35	18.4	14.50	6.01	5.32	-0.69
22	R. I. H.	61.0	6,710	0.169	162	1.56	10.8	16.70	6.06	5.17	-0.89
23	M. I.	16.5	3,840	0.218	295	1.49	12.6	22.00	6.07	5.69	-0.38
24	R. I. H.	19.2	1,710	0.220	192	2.12	35.2	11.41	6.08	5.16	-0.92
25	R. I. H.	41.2	3,400	0.225	160	2.09	37.4	22.20	6.10	5.89	-0.21
26	R. I. H.	18.0	1,110	0.115	655	2.96	13.2	19.00	6.13	5.29	-0.84
27	P. B. B. H.	59.1	1,410	0.257	111	1.67	29.1	18.13	6.19	5.11	-0.58
28	R. I. H.	59.1	5,000	0.170	276	1.53	38.9	1.70	6.25	5.71	-0.54

diet beyond his tolerance, so that he showed sugar constantly and was on the decline. He reentered the hospital June 9, 1916, in poor condition. His physical examination was negative. His urine contained sugar and diacetic acid. There was a trace of albumin but no casts. The carbon dioxid tension of his alveolar air was 21 mm. His blood was strikingly lipemic. He was fasted for nine days with benefit to his acidosis and lipemia, although his glycosuria persisted. It seemed wise to interrupt his fast for four days by allowing a protein-fat diet of 1,000 calories. During this period he developed a tremendous edema so that he looked like a case of chronic nephritis. His color grew pasty, there was edema of his eyelids and genitals, as well as of his entire body.

A second fast for three days cleared his glycosuria. He was then given carbohydrates in the form of green vegetables to the point of tolerance, and finally a mixed diet of 1,700 calories containing 85 gm. of protein and 15 gm. of carbohydrate. He was discharged on this diet, sugar-free and acid-free. Repeated renal function studies were made up to and during the edema formation. They are shown in Table 8.

TABLE 8.—

Date	Weight, Kg.	Diet	Chlorid Intake	24 Hr. Urine	Blood Uren	Urea Index	Sugar		
							Gm. per Liter C	Gm. per 24 Hrs. D	Blood Sugar S
6/10/16	42.0	Mixed observa-	10.00	2,800	0.215	205	22.20	62.00	2.33
6/12/16	42.0	tion diet	10.00	2,400	0.204	91	6.20	14.90	2.63
6/13/16	42.0	Fasting	10.00	1,600	0.195	78	9.40	15.09	2.56
6/14/16	42.0	Fasting	10.00	1,900	0.180	71	6.90	13.10	3.85
6/16/16	41.6	Fasting	10.00	1,600	0.215	83	12.50	20.00	3.23
6/26/16	50.0	Fasting	10.00	4,000	0.170	62	*	*	2.32
10/ 4/16	47.8	Mixed diet	—	4,900	0.262	210	Negative	Negative	1.22

* Heavy reaction not quantitated.

At the first observation the urea index was high and the patient was excreting chlorid with a plasma chlorid lower than the theoretical. As soon as fasting began the renal function became abnormal. This was shown by a falling urea index, a rising blood sugar with a lowering output, and by a marked chlorid retention and edema. Acidosis as estimated by both the alveolar carbon dioxid and actual amount of acetone in the blood diminished. It was only after the chlorid intake was restricted that the condition improved. Finally normal function returned. The effect of withdrawal of salt on the edema is shown graphically by the accompanying chart.

Two possible explanations of the condition come to mind. One is that the acetone bodies exert a specific effect on the kidneys. In support of this, there was presumably a considerable accumulation of acetone bodies in the tissues when the edema was at its height. Although the plasma bicarbonate was normal, the plasma acetone increased, which, according to Marriott³⁹ and Sassa,⁴⁰ shows that the

39. Marriott: Jour. Biol. Chem., 1914, 18, 507.

40. Sassa: Biochem. Ztschr., 1914, 59, 362.

acetone content of the organs was increased as well. Another explanation is that the patient had a true nephritis which cleared up under treatment. In either event the case illustrates the importance of following the chlorid balance in cases with edema.

Another factor of importance in the development of edema in diabetes is the manner in which the body reacts to sodium bicarbonate. It has been recognized that healthy individuals as well as diabetics will develop edema after they have taken continued large doses of the drug. Widal, Lemierre and Cotoni⁴¹ followed the output of sodium chlorid in a patient who was given a known diet, and at the same time the body weight, the development of edema, and its connection with the intake

—CASE R. I. H.. 2394

Chlorid					Alveolar CO ₂ , Mm	Total Blood Acetone Bodiest (Gm. Acetone per Liter)	Urinary Findings
Gm. per Liter C	Gm. per 24 Hrs. D	Plasma Chlorid Cl	Calculated Plasma Chlorid	Difference			
2.75	7.70	5.67	5.89	—0.21	20.2	0.842	Albumin trace; no casts
1.74	4.17	5.40	5.80	—0.40	23.0	0.842	Albumin trace; few casts
1.35	2.16	5.35	5.74	—0.39	26.3	0.851	Albumin trace; few casts
1.15	2.18	5.48	5.73	—0.25	30.8	0.627	Albumin trace; no casts
1.30	2.08	5.27	5.73	—0.46	36.2	0.590	Albumin trace; no casts
0.50	2.00	5.58	5.70	—0.12	43.9	0.270	Albumin negative; no casts
—	—	6.25	—	45.6	0.000	Albumin negative; no casts

† Blood acetone bodies determinations were made on plasma by Marriott's nephelometric method.

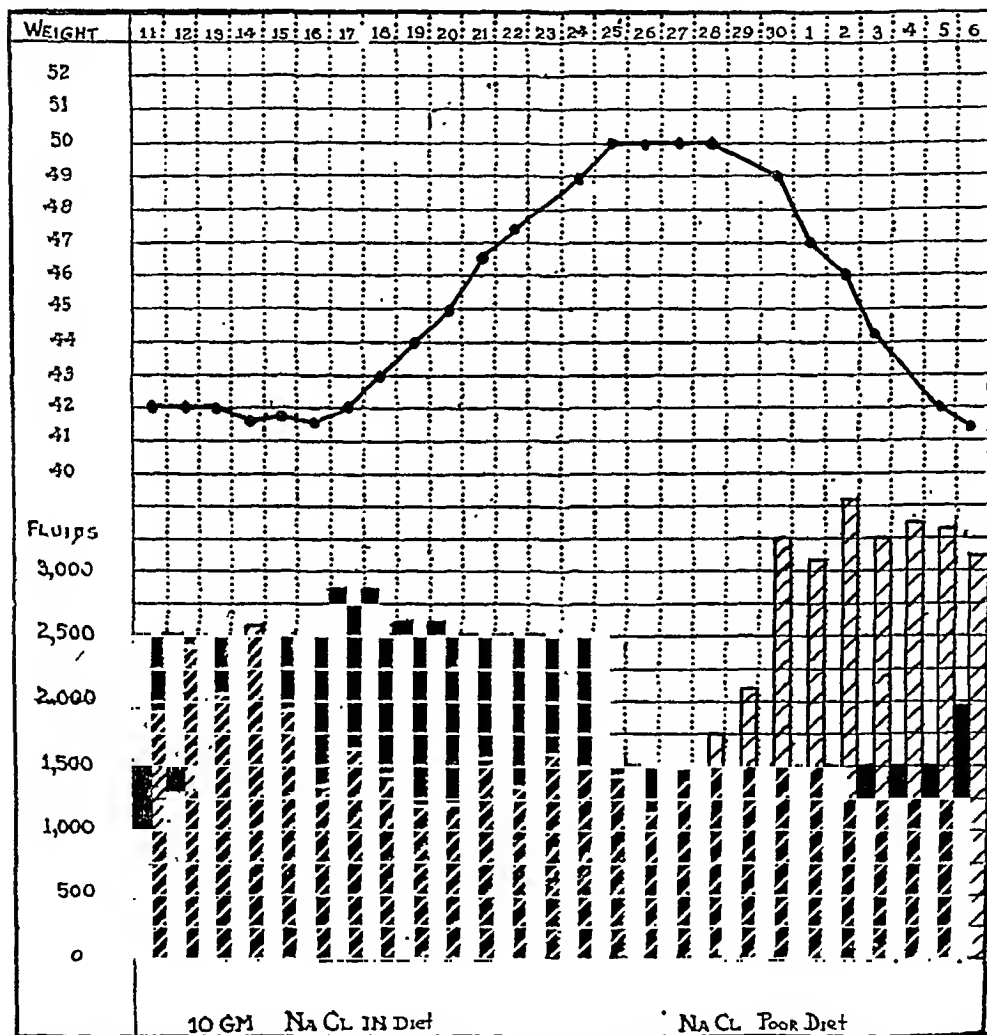
of sodium bicarbonate. They were able to demonstrate that when bicarbonate was given, the excretion of chlorid decreased and edema occurred. When the bicarbonate was discontinued, an excess of chlorid was excreted and the edema disappeared. From this they concluded that bicarbonate edema was not different from other edemas and depended on chlorid retention. The two cases reported in Table 9 would tend to confirm these observers.

In each case the plasma chlorid was lowered after the ingestion of an alkali, and, coincidentally, the rate of chlorid excretion in the urine. Since normal chlorid excretion bears a definite relationship to the plasma chlorid content, any agent lowering the latter would tend to suppress the output of the former. If large amounts of sodium chlorid were taken, and were not excreted on account of a plasma chlorid lowered by alkali, edema would naturally result.

41. Widal, Lemierre and Cotoni: *Semaine méd.*, 1911, **31**, 325.

SUMMARY

Observations on renal function were made in a series of cases of diabetes mellitus. Urea excretion was studied by the urea index of McLean. Chlorid excretion in relation to its concentration in the blood plasma was studied by Ambard and Weill's constants. In addition, observations were made on the effect on renal function of varying degrees of acidosis, hyperglycemia and glycosuria.



Graphic representation of the effect of the withdrawal of salt from the diet on the edema in Case R. I. H. 2394.

The urea index in the majority of cases tended to be normal or abnormally high. This was in part due to the rapid rate of water elimination which characterized many of the cases. Such diuretic effect was not dependent on acidosis or glycosuria, but seemed to be more or less associated with hyperglycemia.

The urea index in six cases of fatal diabetic coma was abnormally low. Renal function appeared to become progressively worse as the

TABLE 9.—THE EFFECT OF SODIUM BICARBONATE ON THE ALVEOLAR AIR.
PLASMA CHLORID AND CHLORID EXCRETION, CASE R. I. H., 2680
CALCULATED SODIUM CHLORID IN PLASMA

CALCULATED SODIUM CHLORID IN PLASMA					
Date	24 Hr. Urine Rate of Excretion	Sodium Chlorid Output Rate of Excretion in 24 Hrs.	Plasma Chlorid	Alveolar CO ₂ , Mm.	Remarks
10/16/15	2,000	3.40	6.01	20.1	50 gm. sodium bicarbonate
10/16/15	4,272	2.56	5.63	33.6	
10/17/15	2,000	0.80	5.85	28.7	20 gm. sodium bicarbonate
10/18/15	6,800	0.68	5.37	41.4	
10/19/15	2,200	1.32	5.58	30.1	15 gm. sodium bicarbonate
10/20/15	2,650	1.34	5.26	39.5	
10/21/15	5,000	Traces	5.23	44.1	10 gm. sodium bicarbonate
10/25/15	4,900	2.45	5.82	39.9	
Case R. I. H., 2128					
3/20/16	5,690	14.20	5.93	23.2	50 gm. sodium bicarbonate
3/21/16	5,000	8.40	5.99	23.0	
3/21/16	3,000	2.22	5.35	38.6	
3/22/16	4,400	6.50	5.89	39.0	
3/24/16	3,635	4.62	5.97	33.2	

coma persisted. One patient had a pronounced accumulation of acetone in the blood plasma without a corresponding increase in excretion, and five patients showed a glycemia which seemed proportionally higher than the corresponding glycosuria. These cases suggest that fatal diabetic coma is accompanied by impaired renal function in which more than one of the kidney's functions are involved. The cause of the complication is not known.

In diabetes the blood plasma chlorid is usually lower than would be calculated from the chlorid excretion according to the formula of Ambard and Weill. This abnormality of excretion is not necessarily associated with acidosis, an abnormal urea index, the degree of glycemia or glycosuria.

Edema due to sodium chlorid retention may be encountered in diabetes. In one case it was accompanied by a falling urea index and by an increase of acetone in the blood without acidosis, as evidenced by an abnormally low alveolar carbon dioxid tension. The edema cleared up promptly when the sodium chlorid intake was restricted.

Edema following the administration of sodium bicarbonate is probably due to sodium chlorid retention, as the plasma chlorid diminishes and at the same time the excretion of sodium chlorid in the urine is lessened when the drug is given.

BOOK REVIEWS

PATHOGENIC MICRO-ORGANISMS. A Practical Manual for Students, Physicians, and Health Officers. By William Hallock Park, M.D., and Anna Wessels Williams, M.D., assisted by Charles Krumweide, Jr., M.D. Sixth Edition. Lea and Febiger, 1917.

The present edition of this well-known textbook conforms, as might be anticipated, in every way to the type of its respected predecessors. Indeed, it seems superfluous to review, and presumptuous to criticize, a book which has become so universally popular. Although written along the general lines of many textbooks of bacteriology, and containing essentially the same material, the wide experience of the authors with the practical as well as the purely scientific side of the work places a stamp of authority on many aspects of the subject which is usually lacking in similar treatises.

It is apparent throughout that real criticism has been exercised in handling the material. Thus, in the sections on technic, staining, and culture mediums the methods of actual value are emphasized, and hand in hand with the presentation of the theoretical side of immunity reactions are given excellent summaries of the technic and actual results of the various practical applications of these principles to diagnosis and treatment. Complement fixation in syphilis and other diseases, anaphylaxis and serum sickness, the opsonic index, ferments and antiferments, and leukocytic extracts are examples of the questions discussed. The sections on vaccine and serum therapy assume a rather liberal point of view, but one could hardly be more conservative without courting controversy. The remarks on diphtheria antitoxin are particularly concise and authoritative.

The sections on the systematic discussion of the various pathogenic micro-organisms are clear and succinct, and the results of recent studies have been incorporated. Thus the division of pneumococci into groups by biologic reactions, the question of the virulence of diphtheria bacilli in relation to carriers, and the use of the Schick test may be mentioned among the many topics treated. One is interested to note the inclusion of the bacillus of Plotz as the cause of typhus fever.

The outlines of the bacteriologic examination of milk, water and foods, and the section on disinfectants include the methods which have been found valuable by the authors in connection with the work of the New York Health Board. The Carrel-Dakin method of disinfecting wounds is presented here probably for the first time in a general text.

The references, finally, should be invaluable to the student as leads for looking up the various subjects.

The Archives of Internal Medicine

Vol. XX

DECEMBER, 1917

No. 6

STUDIES OF THE HEART'S FUNCTIONAL CAPACITY*

THEODORE B. BARRINGER, JR., M.D.
NEW YORK

The term functional capacity is used to indicate the total amount of power possessed by the heart muscle. When the body is at rest a small portion of this power is utilized to furnish the circulatory requirements of the metabolism. As soon as any muscular activity occurs the so-called reserve power of the heart is drawn on to furnish blood to the working muscles.

Of these two component parts of the power inherent in the heart muscle the reserve power forms normally by far the larger portion, and it is with this factor that our studies are concerned. We propose to gain an idea of the heart's functional capacity by a measurement of its reserve power.

The method used to determine this is based on the circulatory reactions to graduated work, and a rather detailed description of these reactions is necessary to a clear understanding of our test, and, what is more important, to a belief in its validity.

Work was furnished by means of a Krogh-Lindhard ergometer in a few experiments, but in the greater number by movements with dumb-bells. The blood pressures were taken by the auscultatory method with a Riva Rocci manometer. A rubber hand bulb was used to inflate the cuff. The systolic pressure and pulse were taken and then work was performed. The pressure was read again between twenty and thirty seconds after completion of work. This was the time required with our technic to make the first reading, and 90 per cent. of the readings on the first trial fell between 20 and 30 seconds. If the first reading was made before twenty seconds or after thirty seconds had elapsed the experiment was discarded. A second reading was made between 50 and 60 seconds after work, the aim being to make it as close to 60 as possible, and the third reading 90 seconds after. Then readings were made every 60 seconds. (In our earlier experiments we made readings every 60 seconds after the first reading; later we made readings every 30 seconds after.)

* Submitted for publication June 12, 1917.

* From the Second Medical Division of the New York Hospital.

* Read before the Section on Practice of Medicine at the Sixty-Eighth Annual Session of the American Medical Association, New York, June, 1917.

In a person with normal heart, shortly after work the systolic blood pressure and pulse rate are increased. If they are then taken according to the above plan they will be found to return rapidly to the figures noted before work. If successively increasing amounts of work are performed the same reactions will be observed. The greater the work, the higher are the subsequent systolic pressure and pulse rate. Finally, an amount of work is reached which is followed by a different type of blood pressure curve. It does not reach its greatest height within thirty seconds after the completion of work, but at a later period (fifty to ninety seconds) when the pulse rate has dropped back toward normal.

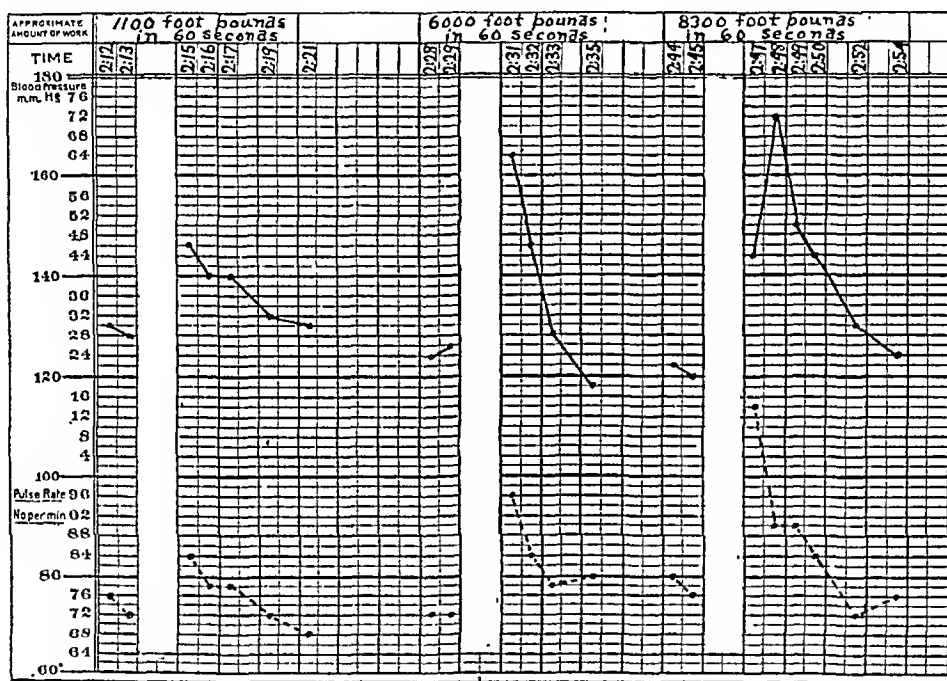


Chart 1.—Circulatory reactions in a normal man to increasing amounts of work performed by means of dumb-bells. The white perpendicular spaces represent the work periods in each experiment during which blood pressure and pulse rate could not be measured.

Chart 1 represents the course of the blood pressure curve in a normal individual after increasing amounts of work, which were furnished by dumb-bell exercises.

This delayed rise in systolic pressure (for so we shall term it) is a most interesting and extraordinary phenomenon. It has been the subject of many hundred experiments on both normal persons and patients with cardiac insufficiency, and we shall summarize the facts we have discovered about this peculiar reaction.

1. It is always obtained in normal people whenever the work exceeds a certain amount (the work may be of any kind).

2. Children are able to do much larger amounts of work, in comparison to their weights than are adults before a delayed rise ensues.¹

3. It makes no difference what group of muscles is employed to do the work. If, for example, a delayed systolic rise follows 5,000 foot-pounds of work, performed in sixty seconds with the arm and back muscles, it will invariably follow 5,000 foot-pounds of work done in sixty seconds with the thigh and leg muscles. It is the amount of work and the time in which it is performed, or, technically, the power expended, which determine the delayed rise, not the group of muscles used.

4. The amount of work which is followed by a delayed rise varies but slightly from day to day in the same individual.

5. Patients with varying grades of cardiac insufficiency are able to perform much smaller quantities of work than normal individuals before a delayed rise ensues. These quantities are measured in hundreds, as compared with thousands in normal individuals. Occasionally in these cardiac patients the pressure after work is lower than before. It then rises to or even above the original figures.

6. Patients with marked cardiac insufficiency, edema, dyspnea when resting, etc., are able to do no work at all which is not followed by a delayed rise or fall.

7. As the general health of normal persons improves, or as the condition of cardiacs improves, we find that the amount of work which can be performed before a delayed rise ensues becomes greater and greater.

8. In a few experiments on patients with cardiac insufficiency we have found that digitalis causes a marked but temporary increase in the amount of work the patient can do before a delayed rise ensues.

9. In the treatment of normal people, and of cardiacs by graduated exercises, the prescribing of quantities of work which are not followed by delayed rises has caused a marked improvement in the majority of suitable cases.

Of all these facts the most significant is, perhaps, the one which shows that the delayed rise occurs quite independently of the group of muscles used in the work.

Charts 2 and 3 illustrate this most important point.

Gräupner described the delayed rise many years ago, but he did not discover its most significant feature, which has just been described.

The present incomplete state of our knowledge of circulatory physiology does not permit of a complete explanation of the phenomenon.

1. The data on which this statement is based were furnished through the courtesy of Drs. W. P. St. Lawrence and H. L. Bibby.

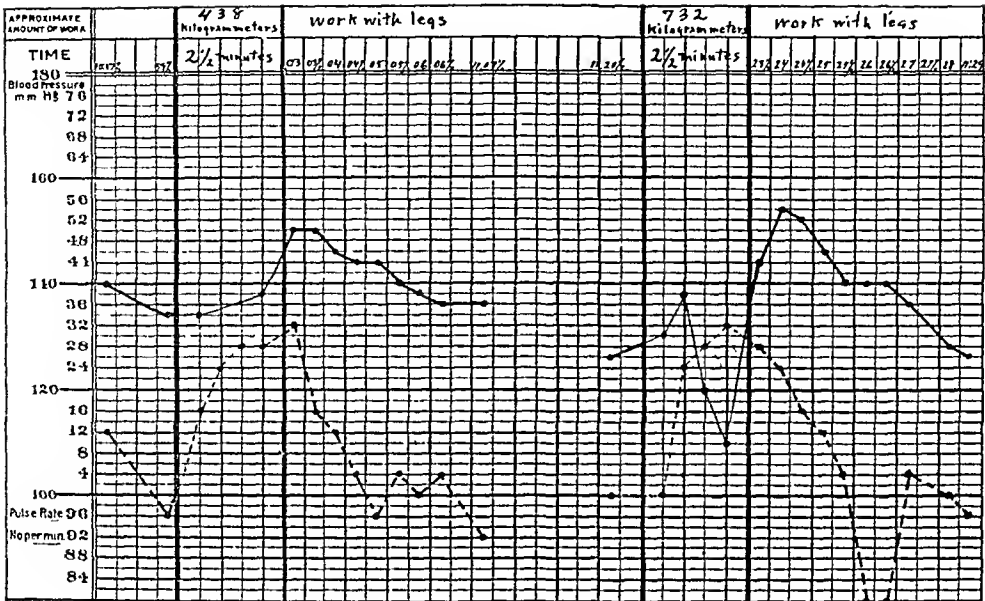


Chart 2.—Circulatory reactions in patient C. G. suffering from cardiac insufficiency to increasing amounts of work performed with the legs on the bicycle ergometer.

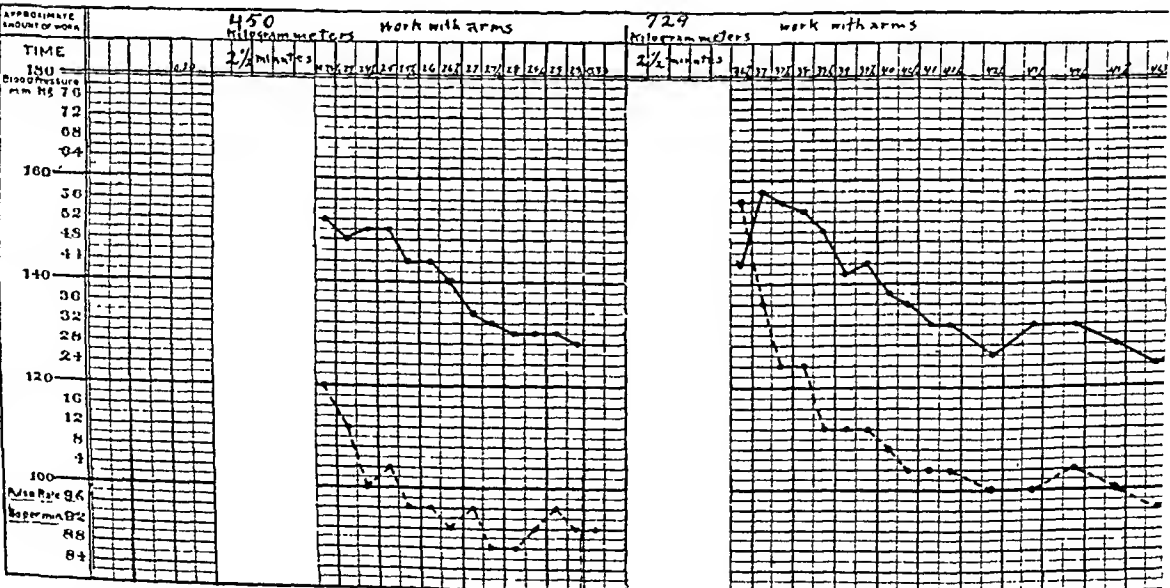


Chart 3.—A continuation of the experiments shown in Chart 2 on the same patient a few minutes later, the work being performed on the bicycle ergometer with the arms instead of the legs. The white perpendicular spaces represent the work periods in each experiment during which blood pressure and pulse rate could not be measured.

If its significance is to become apparent it can only do so at present through clinical experiments.

We believe that the facts here enumerated, many of which have been confirmed by other observers, demonstrate, as far as it is possible to demonstrate clinically, that the delayed rise in systolic pressure indicates that the preceding work has exceeded the limit of the heart's reserve power.

We conclude, therefore, that if the systolic blood pressure does not reach its greatest height during the first thirty seconds after the completion of work, but at the second or third reading (that is, fifty to ninety seconds after work), or if this first reading is lower than the original level, that work, whatever its amount, has overtaxed the heart's reserve power and may be taken as an approximate measure of the heart's reserve power.

In the following studies we have considered work which was not followed by a delayed systolic rise as being within the heart's reserve power, and work which was followed by a delayed rise as exceeding the heart's reserve power.

We have used various movements with iron dumb-bells, which were first described by Dr. Jacob Teschner of New York, to furnish work, on account of their convenience and the ease of making comparative estimations of the amount of work performed.

STUDIES OF THE HEART'S RESERVE POWER IN NORMAL INDIVIDUALS

Chart 4 summarizes our results by decades in forty-five normal persons.

Effect of Digitalis on the Cardiac Reserve Power in Normal People and in Patients with Cardiac Insufficiency.—Three people were selected with normal hearts but low reserve powers: One, aged 52 years, had pulmonary tuberculosis and had a reserve power averaging from day to day between 500 and 600 foot-pounds performed in thirty seconds. One, aged 43 years, had a chronic pyloric ulcer with partial gastric retention and averaged between 250 and 300 foot-pounds in fifteen seconds. The third, aged 51 years, had a cancer of the esophagus and averaged between 150 and 200 foot-pounds in fifteen seconds. Their hearts were normal on physical examination and showed normal electrocardiograms. They all received large doses of digitalis, enough to produce mild toxic symptoms, but showed no increase whatever in their cardiac reserve powers.

A fourth patient, aged 23 years, suffering from rheumatic endocarditis and slight cardiac insufficiency, which was evinced by some

dyspnea on climbing stairs, showed a marked, but temporary, increase in his heart's reserve power following digitalis.

Chart 5 represents this experiment.

Effect of Graduated Exercises on Normal Hearts and on Cardiac Insufficiency.—Chart 6 illustrates the effect of daily graduated exercises with dumb-bells on a patient with low reserve power, due probably to a combination of hard intellectual work, no exercise, insomnia, several attacks of bronchitis, and much tobacco and considerable alcohol. Physical examination of the heart and the electrocardiogram were normal.

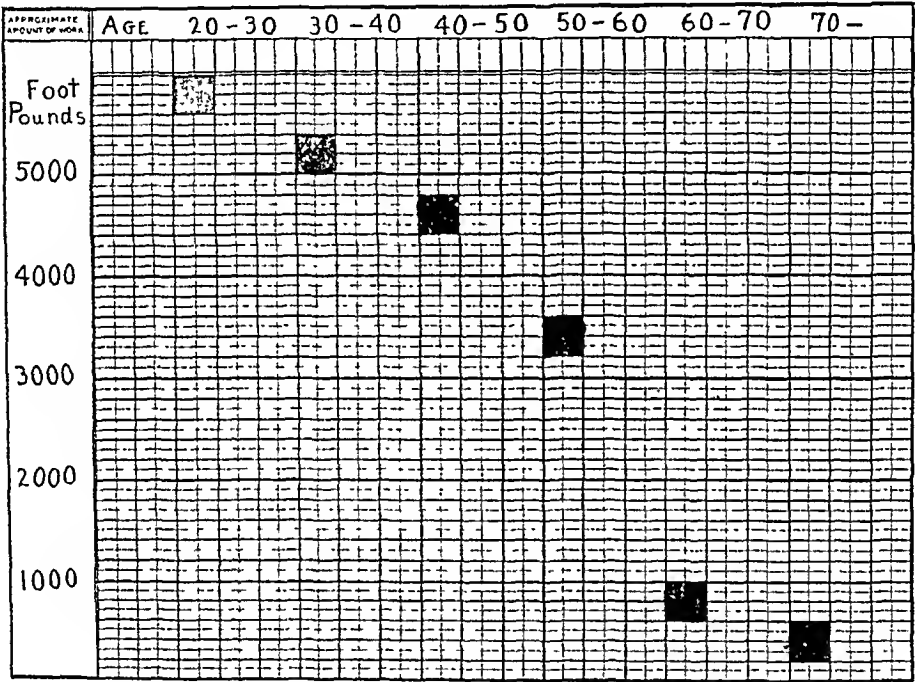


Chart 4.—Average cardiac reserve power by decades of forty-four normal adults. Each space between two heavy perpendicular lines represents sixty seconds. The black squares represent the heart's capacity. For example, between the ages of 20 and 30 years the average heart was able to supply sufficient blood to the muscles to enable them to do 5,600 foot-pounds in sixty seconds. The performance of 6,000 foot-pounds was followed by a delayed rise. It will be noted that the highest figures were obtained between the ages of 20 and 30 years. After that the heart's reserve power steadily decreases.

Chart 7 represents the effect of daily graduated exercise on a patient, J. C., suffering from cardiac insufficiency. He was 54 years old and had had his first attack of cardiac insufficiency in 1913, having at that time swelling of the feet and legs and dyspnea. Sept. 8, 1915, he was admitted to the House of Relief with the same symptoms. He was a thin man with gray hair, dyspnea and with markedly swollen legs and scrotum. The heart was enlarged and showed an aortic and

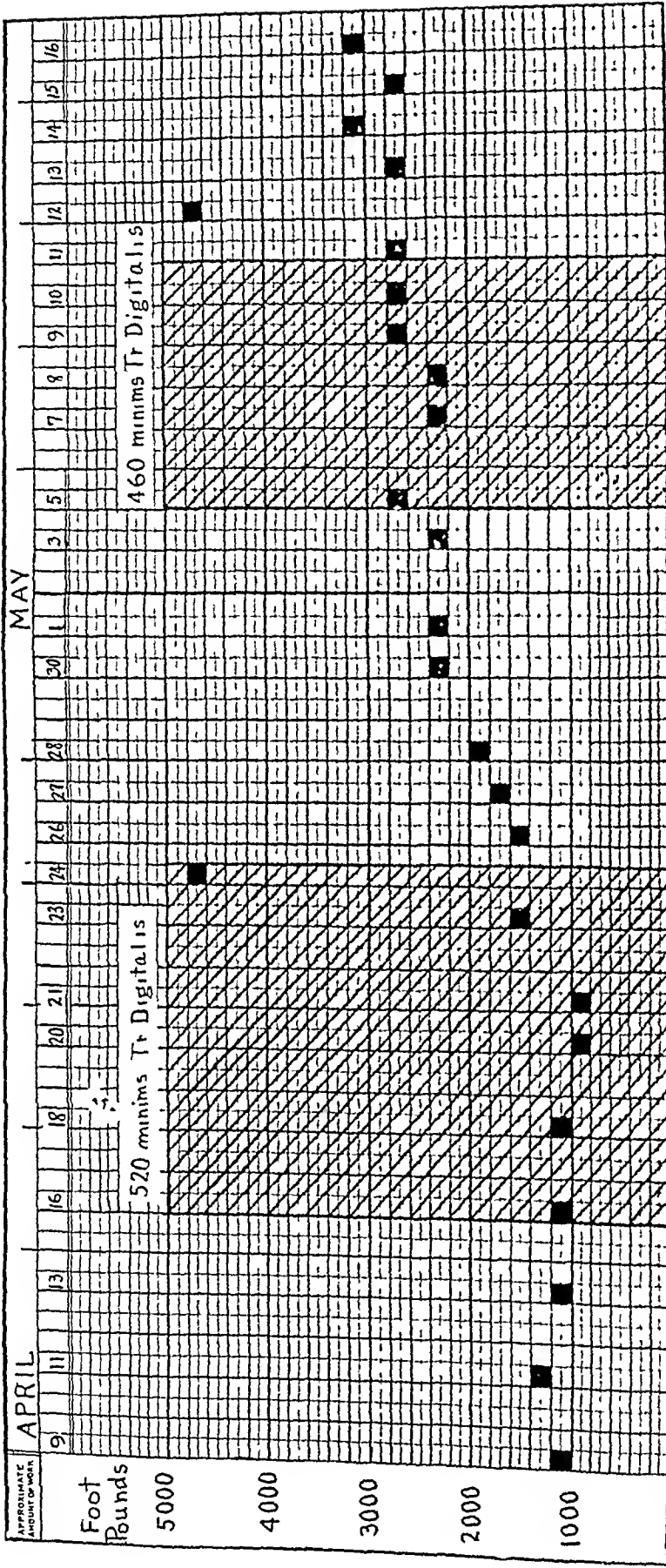


Chart 5.—Effect of digitalis on cardiac insufficiency. Each space between two perpendicular lines represents thirty seconds. The black squares represent the heart's reserve power. The shaded portions represent the periods during which digitalis was given. It will be noted that the heart increased its efficiency rather suddenly on both occasions at a time when the digitalis had produced a toxic effect.

mitral regurgitation. There were signs of small quantities of fluid in both pleural cavities. The liver was enlarged and the blood showed a four plus Wassermann reaction. He received altogether 16 dr. of tincture of digitalis and twenty intramuscular injections of mercury salicylate. September 22, the cardiac capacity was tested and the patient was given a course of graduated exercise. A few days after the exercise began the digitalis was stopped.

September 22, when he was able to walk slowly around the ward for a short distance, his cardiac capacity was very low. December 27,

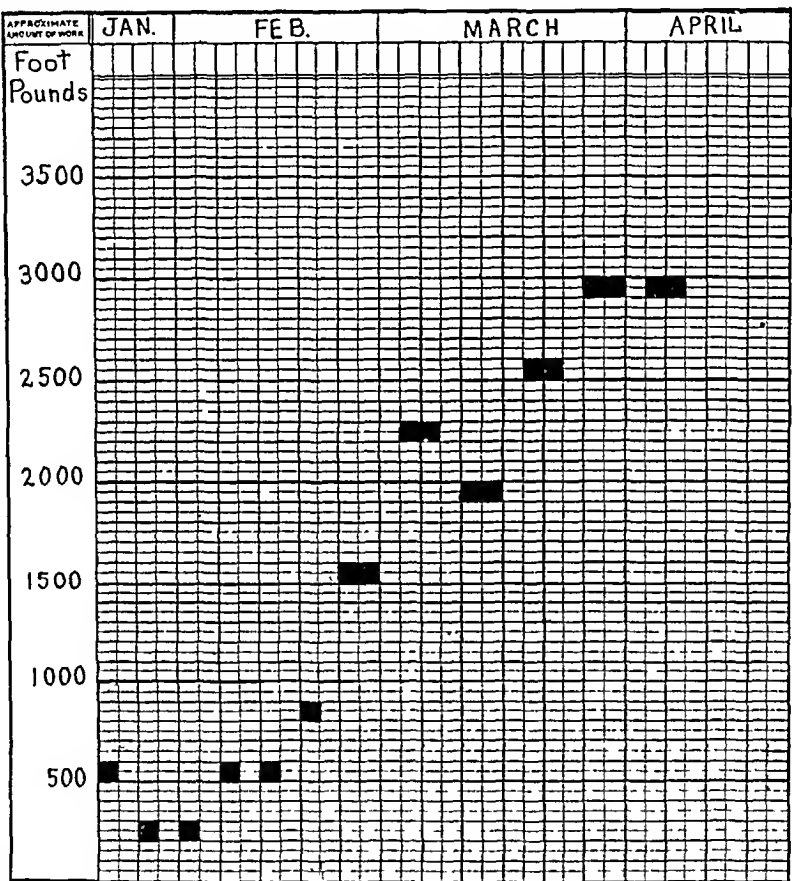


Chart 6.—Course of the heart's reserve power in normal individual A. O. In this chart each space between two consecutive perpendicular lines represents fifteen seconds. The black squares represent the heart's capacity.

when his capacity had increased to between 900 and 1,100 foot-pounds performed in sixty seconds, he was much stronger and able to do light work.

It can be gathered from the studies described here that the cardiac reserve power may be very low in a man with perfectly normal heart as well as in a man with diseased heart. Mackenzie has made the same observations in his last work on the heart, although his conclusions were reached without the aid of any test of the heart's reserve power.

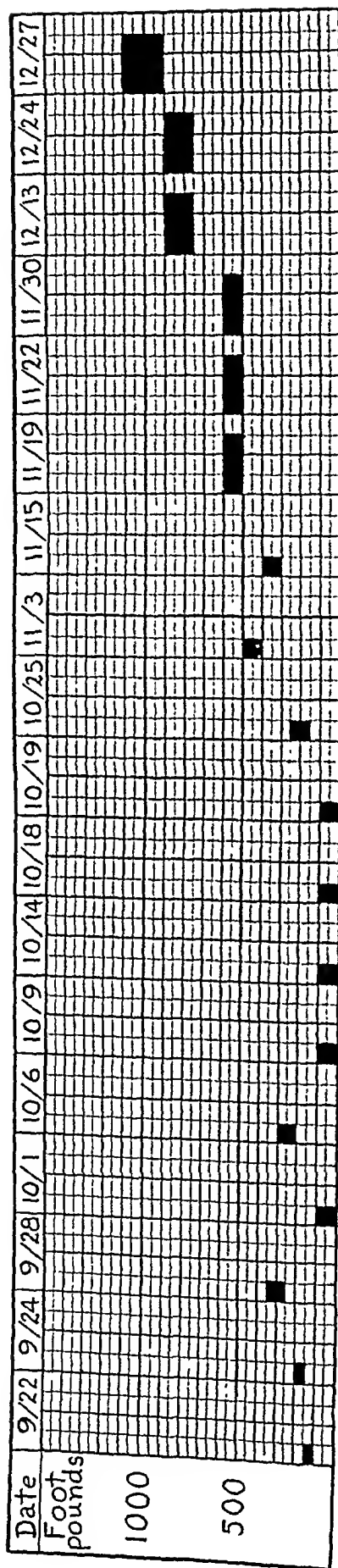


Chart 7.—Course of the heart's reserve power in J. C., suffering from aortic regurgitation and cardiac insufficiency. In this chart each space between two consecutive perpendicular lines represents fifteen seconds.

The simplicity of the test of the heart's reserve power on which the foregoing studies are based, puts it within the reach of every practitioner. A few experiments will enable any one to confirm the most important of the circulatory reactions we have described. It makes no difference what kind of work is used, stair-climbing, walking, dipping exercises, or dumb-bell work, for any one of these permits of a comparative measure of the cardiac reserve power. It is hardly necessary to point out the value of the information derived through this test, but we will mention one subject which has been much illuminated thereby, namely, the kind and amount of exercise which a cardiac patient may take. Also the bearing it has on the suitability of any particular occupation is obvious. We have advised many cardiacs during the past two years on these two matters and the results have proved to be almost without exception so excellent that we feel this experience affords additional evidence of no slight value in support of the validity of our test.

I wish to express my indebtedness to Dr. William R. Williams, whose cooperation has made much of the preceding work possible, and to Dr. H. E. B. Pardee for his help in the experiments with digitalis, and for doing the electrocardiographic work.

ADDENDUM

I take this opportunity to reply to an article by D. L. Rapport,² entitled "The Systolic Blood Pressure Following Exercise, with Remarks on Cardiac Capacity."

Dr. Rapport conducted experiments on normal people to determine the blood pressure reactions following graduated work. His blood pressure readings were made sooner and more frequently after work than ours were and he was able to show that the systolic rise never reaches its greatest height immediately after work, but at varying subsequent times, depending on the amount of work, thereby differing from our conclusions.

Dr. Rapport was unfamiliar with the technic we have used since early in 1916, which is described above. Our first readings were made between 20 and 30 seconds after the completion of work, the second reading 50 to 60 seconds after work, and the third reading 90 seconds after work. By our method we secured curves of the systolic pressure which were so nearly isochronous that their comparison must have been valid in the great majority of instances. Whenever we detected a delayed rise (and no difference less than 4 mm. of mercury was considered as such) the experiment was not considered valid unless we could obtain the same or a more marked delay in the rise by a repetition with increased work. It seems apparent that when we did get this reaction it must have been a marked example of the phenomenon because our first reading was not made earlier than twenty seconds after work. Otherwise, we would have noted this reaction constantly. Also, if our technic had not been unvarying we could not have obtained the constant results we have described.

34 West Eighty-Fourth Street.

2. Rapport, D. L.: *THE ARCHIVES INT. MED.*, 1917, **19**, 981.

I reproduce one of Dr. Rapport's charts (Chart 8) depicting four reactions which he considers "in most respects characteristic."

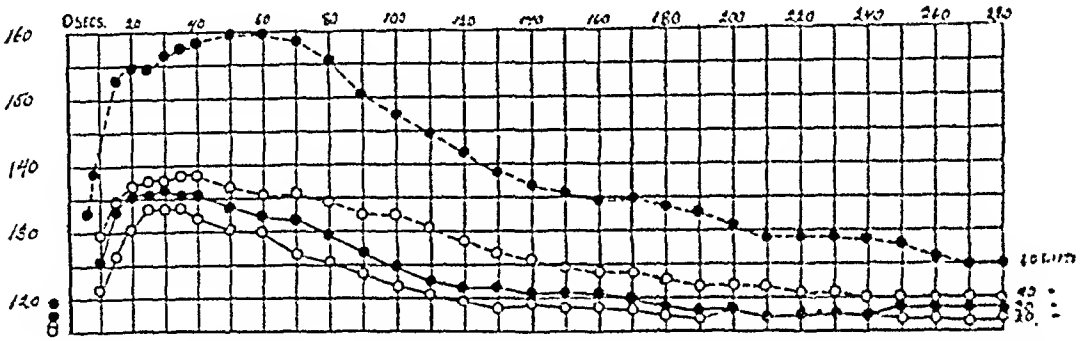


Chart 8.—Weight of subject 140 pounds; lift, two 10-pound dumb-bells through 6 feet; time, one lift in two seconds. With thirty lifts, slight breathlessness; with forty lifts, moderate breathlessness; with sixty lifts, considerable breathlessness and slight distress. As in all curves, the zero mark represents the cessation of exercise, the readings charted to the left of this line being controls taken before exercise.

Compare with this our interpretation of his chart which notes the readings which would have been made by our method (Table).

INTERPRETATION OF DR. RAPPORT'S CHART BY OUR METHOD
OF NOTING BLOOD PRESSURE

Work = 20 Lifts

Time	(Before work) Systolic Blood Pressure, 115
20 seconds.....	130 }
30 seconds.....	134 }
50 seconds.....	130 }
60 seconds.....	130 }
90 seconds.....	124 }

Work = 40 Lifts

Time	(Before work) Systolic Blood Pressure, 115
20 seconds.....	136 }
30 seconds.....	137 }
50 seconds.....	136 }
60 seconds.....	135 }
90 seconds.....	133 }

Work = 30 Lifts

Time	(Before work) Systolic Blood Pressure, 118
20 seconds.....	135 }
30 seconds.....	136 }
50 seconds.....	134 }
60 seconds.....	132 }
90 seconds.....	127 }

Work = 60 Lifts

Time	(Before work) Systolic Blood Pressure, 120	
20 seconds.....	155 }	
30 seconds.....	156 }	
50 seconds.....	160 }	Delayed rise
60 seconds.....	160 }	
90 seconds.....	150 }	

What we term "delayed rise" is apparently identical with what Dr. Rapport terms a "delay in the full development of the rise." Our contention is that this most marked form of reaction, whatever we term it, indicates an over-taxing of the heart's reserve power, and the clinical experiments we have described above are offered as substantiation of this thesis.

FIVE GENERATIONS OF ANGIONEUROTIC EDEMA*

JOSEPH R. CROWDER, M.D.
SULLIVAN, IND.

AND

THOMAS R. CROWDER, M.D.
CHICAGO

What we now call angioneurotic edema was first adequately described by Quincke,¹ in 1882, as "acute circumscribed edema of the skin." He looked on it as a vascular neurosis and attempted to separate it clinically from all other forms of local edema as a distinct disease. But while to Quincke belongs all the credit of having first presented the subject with the detail and interpretation necessary to its general recognition, he was not the first to observe the condition so carefully as to recognize its individual character. This had been done ten years earlier by Milton,² who recorded his observations in 1876 under the title, "On Giant Urticaria," pointing out clearly that the cases were of a new kind to him and were distinctly different from the severest forms of urticaria as previously described and commonly understood. Had he dignified with a new name the new condition he observed so carefully, the recognized literature of angioneurotic edema would no doubt have begun with him.

The nomenclature of angioneurotic edema has been a various one. It has been described under no less than twenty more or less appropriate descriptive titles, such as "giant urticaria," "massive urticaria," "ephemeral congestive tumors of the skin," and "ephemeral cutaneous modosities," while many have called it simply Quincke's disease or Quincke's edema, out of compliment to its discoverer. The term angioneurotic edema was originated by Strübing³ in 1885, and has been the one most commonly used to designate the condition since that time; though perhaps the most extensive reviewer of the subject, Cassirer,⁴ discards it for the simpler one of "acute circumscribed edema," recognizing that there is no final proof of its neurotic origin, that the disease is not confined to the skin, and believing that the name should carry a

* Submitted for publication June 15, 1917.

1. Quincke: *Monatsh. f. pract. Dermat.*, 1882, **1**, 129.

2. Milton: *Edinburgh Med. Jour.*, December, 1876, p. 513.

3. Strübing: *Ztschr. f. klin. Med.*, 1885, **9**, 381.

4. Cassirer: *Vasomotorische trophischen Neurosen*, p. 242. S. Karger, Berlin, 1901; Lewandowsky's *Handbuch der Neurologie*, **5**, 256. J. Springer, Berlin, 1914.

distinction from some ill-understood but possibly related chronic edemas like Milroy's disease and recurrent hydrops of the joints.

Angioneurotic edema is not an uncommon disease. In 1901 Cassirer was able to collect from the literature 160 cases, described under one or another of its various names, and many others have been published since. The disease is characterized by acute, massive, ephemeral swellings of the skin, and sometimes of mucous membranes or of internal organs, which often develop and disappear with great rapidity, leaving no trace behind them. It has a tendency to recur, many of those who suffer from it being repeatedly attacked. It is often associated with other neuroses; and it seems to be more or less closely related to urticaria and other skin lesions exhibiting local vascular disturbances. Osler calls its swellings "only urticarial wheals 'writ large,'" but the typical Quinke's disease, with its large, pale, cool, nonitchy swellings, is in marked contrast to the usual form of urticaria; and unlike urticaria the character of the food seems unimportant as an etiologic factor.

Angioneurotic edema generally appears as an acute sporadic affection without adequate clinical explanation. But as a relative rarity there has been observed a familial type of the disease, in which the affection has seemed to be distinctly hereditary and has appeared in several or many members of a family through two or more successive generations. It is to this type of the disease, the general features and literature of which were well summarized by Fairbanks,⁵ in 1904, that we wish to direct attention.

Shortly after the identification of Quinke's edema in 1882, Dinkelacher,⁶ one of Quinke's students, observed the disease in a watchmaker who had been affected by transient local swellings for many years and who had a son likewise affected from an early stage of infancy. Three years later Valentin⁷ observed in this same family another son, not born at the time of Dinkelacher's report, who was affected from the first week of his life, and a daughter who was free from the disease. In 1885 Strübing⁸ described a case in a man aged 71 years, who had been subject to attacks of swelling of the throat and face from his 26th year, and who had a son and a daughter similarly affected from very early life. A year later Falcone⁹ reported

5. Fairbanks: *Am. Jour. Med. Sc.*, 1904, **127**, 877.

6. Dinkelacher: *Inaug. Diss.*, Kiel, 1882. Reference by Fairbanks, *loc. cit.*, Footnote 5.

7. Valentin: *Berl. klin. Wchnschr.*, 1885, **23**, 150.

8. Strübing: *Ztschr. f. klin. Med.*, 1885, **9**, 381.

9. Falcone: *Gazz. d. osp.*, 1886, **7**, 125. Reference by Fairbanks, *loc. cit.*, Footnote 5.

a case of acute recurring edema in a child of 7 years whose grandfather suffered similar attacks.

Osler¹⁰ first called attention to the existence of hereditary angioneurotic edema in this country, in 1888. He published the history of a family in which it was present through five generations, and in which twenty-two members had suffered from repeated attacks of the disease. Long after the publication of his original report, Osler¹¹ had the opportunity of examining two members of the sixth generation of this family who also had the disease. The condition was characterized by the occurrence of transient local swellings in various parts of the body which were almost always accompanied by gastro-intestinal disturbances, such as colic, nausea, vomiting and sometimes diarrhea.

Others who have added to the list of cases of the familial type of angioneurotic edema are: Kreiger¹² who, in 1899, reported cases in a mother and son; Fritz,¹³ 1893, who recorded a history in which eight members of one family were subject to severe attacks, and five of whom died of edema of the glottis; Roy,¹⁴ 1894, who observed the disease in a mother and daughter; and Ricochon,¹⁵ 1895, who saw three generations of one family affected, the attacks being accompanied by colic, vomiting and fever. Yarian,¹⁶ in 1896, described a case in a woman of 42, with a history of nine other cases among relatives; Schlesinger,¹⁷ 1898, reported on a family which was affected through four generations; Griffith,¹⁸ 1902, saw a father and daughter who died of the disease, with acute edema of the larynx, at the respective ages of 29 and 23; Harris,¹⁹ 1905, observed the disease in a patient aged 21 years, who had twice been tracheotomized for laryngeal edema (which ultimately proved fatal) and whose mother and sister were likewise affected; and Harbitz,²⁰ 1911, described a case where there was a history of similar attacks in a brother, the father, the paternal grandfather, and in two sisters of the grandfather.

Unusual and extensive were the ravages of the disease in a family observed by Ensor,²¹ where among eighty members in three gen-

10. Osler: *Am. Jour. Med. Sc.*, 1888, **95**, 362.

11. Osler: *Modern Medicine*, Ed. 2, 1915, **4**, 998.

12. Kreiger: *Meditzinskivie Oborzrenie*, 1889. Reference by Fairbanks, loc. cit., Footnote 5.

13. Fritz: *Buffalo Med. and Surg. Jour.*, 1893-1894, p. 286.

14. Roy: *Med. Rec.*, New York, 1894, **66**, 42.

15. Ricochon: *Semaine méd.*, 1895, p. 365.

16. Yarian: *Med. News*, London, 1896, **69**, 238.

17. Schlesinger: *Wien. klin. Wchnschr.*, 1898, No. 14, p. 335.

18. Griffith: *Brit. Med. Jour.*, 1902, **1**, 1470.

19. Harris: *Am. Jour. Med. Sc.*, 1905, **130**, 382.

20. Harbitz: *München. med. Wchnschr.*, 1911, **58**, No. 48.

21. Ensor: *Guy's Hosp. Rep.*, 1904, **58**, 111.

erations thirty-three were attacked and twelve died of edema of the glottis.

Unless other and more extensive reports have escaped our notice, it would seem that the opportunity to observe angioneurotic families and to study the history of their trouble through successive generations does not often come to physicians. The history of such a family which has come under our observation may therefore be of sufficient interest to warrant its publication.

In the community where one of us (J. R. C.) resides there has been for many years a family in which the frequent occurrence of local swellings in various parts of the body is a fact of common knowledge to their friends and neighbors and a matter of grave concern to the parents of children who may become victims of this hereditary weakness. Many of the members of this family have suffered severely and repeatedly through longer or shorter lives, and not a few have finally died the victims of attacks in vital organs. The disease is known to have continued through five generations.

Only one of the affected members of this family has come under our personal observation as a patient. He is now nearly 80 years of age. Since early life he has been subject to severe attacks of local edema, sometimes of monstrous size, developing quickly, disappearing with equal rapidity, and affecting at different times practically all parts of the surface of the body. In his later years these attacks have been infrequent and of slight severity, but through all of his early adult and middle life they were both frequent and severe. He was never able to foretell them more than a very short time before the swelling began, and was never able to associate them with any particular event, either dietary, traumatic, or otherwise. They come out of nowhere, and disappear with equal mystery. There is sometimes disturbance of the digestive system, but it has no constancy. He says that before the swelling begins there may be a little tingling or burning, but rarely a genuine pain, and that with full development there is only a local feeling of fulness and tension. With the attacks there is always a sense of anxiety and uneasiness, and a fear born of painful knowledge of misfortune in many of his relatives that the trouble will "strike to the throat." There is a family tradition that the immediate adoption of heroic treatment with alcoholics and nitroglycerin will combat the cause and cure the attack. And, indeed, it has seemed to do so many times; but whether the relation of cause and effect is properly judged in this there would seem to be much doubt.

The family history, in so far as it concerns the appearance of angioneurotic edema, begins with the father of our patient. About 1820, being then a young man and recently married, J. C. took a contract in the logging camps of western Pennsylvania. The winter was very cold, with much snow on the ground, and he lived under the primitive conditions to be found in loggers' cabins. During this winter he had an attack of illness which was subsequently referred to as quinsy, in which the neck was greatly swollen. From that time on swellings were repeated at irregular intervals, invading all parts of the body, and they were eventually fatal through involvement of the throat, though not until the lapse of something like twenty years. Previous to his attack in the logging camps he had never suffered with any such malady, nor, so far as was ever known to him, was there any history of a similar affection in his immediate family or among any of his relatives.

This man was the father of ten children, three daughters and seven sons, of which our patient was next to the youngest. Though the mother of these children was entirely free from their father's affliction, his peculiar malady was transmitted to all of them with the exception of one son, and seven of them are said to have died of the disease. Two of the affected nine of the

second generation died without descendants; to the remaining seven there were born twenty-nine children, and twelve of these twenty-nine had angioneurotic edema. In only one of the seven groups of children born to these seven affected parents, and making up the third generation, were all the children free from the disease. In the fourth generation there are seven known groups of children with a total of eighteen individuals. Nine of these children are descended from three unaffected parents and are free from the disease. Nine are descended from four affected parents and five have the disease. Only one of the affected parents gave issue to children who have thus far entirely escaped. The fifth generation contains only six known members up to the present. Three are the daughters of an unaffected mother and are free from the disease; three are the daughters of an affected mother, and one of them has the disease—the only case so far observed in the fifth generation.

In this family, so far as it can be traced from the first to the fifth generation, definite histories have been obtained of sixty-four individuals. Among them there have been twenty-eight cases of angioneurotic edema and fifteen deaths from an acute form of the disease. That is, of the sixty-three known descendents of J. C. twenty-seven, or 42.9 per cent., have inherited his disease, and 51.5 per cent. of those who have had the disease have died of it. Both the descendents of J. C. and the cases of angioneurotic edema among them have been about equally divided between males and females. Of the former there have been thirty-two, with thirteen, or 40.6 per cent., affected; of the latter there have been thirty-one, with fourteen, or 45.2 per cent., affected. Their distribution by generations is shown in Table 1.

TABLE 1.—DISTRIBUTION BY GENERATIONS

Generation		Males	Females	Total
II	Affected	6	3	9
	Not affected	1	0	1
	Per cent. affected.....	85.6	100.0	90.0
III	Affected	5	7	12
	Not affected	12	5	17
	Per cent. affected.....	34.0	58.4	41.4
IV	Affected	2	3	5
	Not affected	6	7	13
	Per cent. affected.....	25.0	30.0	27.8
V	Affected	0	1	1
	Not affected	0	5	5
	Per cent. affected.....	16.6	16.6
Total	Affected	13	14	27
	Not affected	19	17	36
	Per cent. affected.....	40.6	45.2	42.9

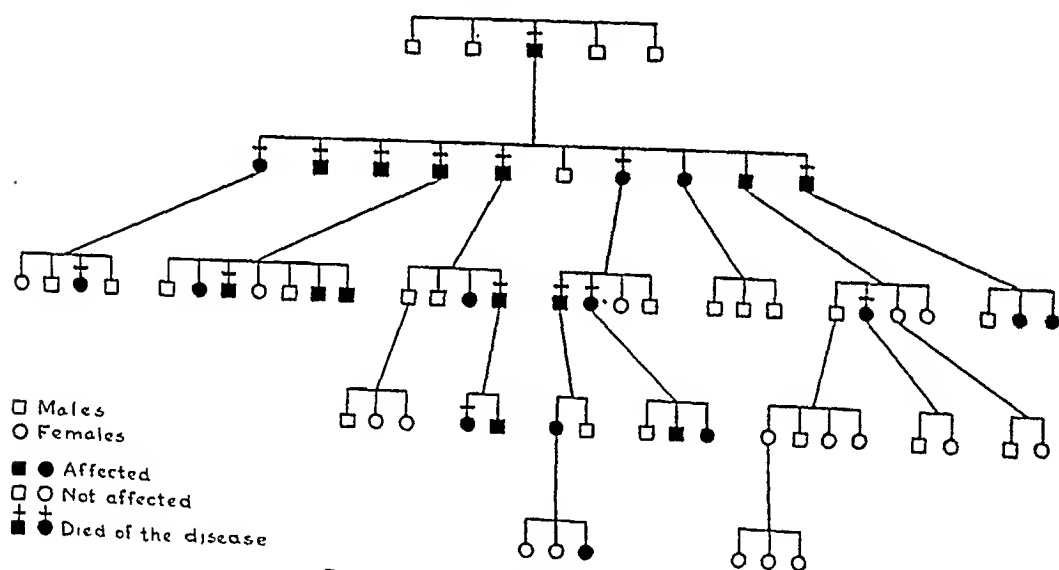
If we confine our attention to the children of affected parents only, it is found that 53 per cent. of them have inherited the parents' affliction. Confining it so, the details of the inheritance by generation and through the two sexes are shown in Table 2, in which the figures in parenthesis indicate the number of affected parents concerned.

From the figures in the last group in Table 2 it would seem that the inheritance is twice as likely to occur through the male as through the female line; but if we eliminate the children of the first affected father,

that is, the second generation, the difference is found to be rather less, though still striking. There is an instance in the literature, recorded by Cassirer,²² in which the inheritance was entirely through the male line.

TABLE 2.—DETAILS OF INHERITANCE FROM AFFECTED PARENTS

Generation		Fathers	Mothers	Total
II	Total children of affected parents	10 [1]	10 [1]
	Affected children.....	9	9
	Per cent. of children affected....	90.0	90.0
III	Total children of affected parents	18 [4]	11 [3]	29 [7]
	Affected children.....	9	3	12
	Per cent. of children affected....	50.0	17.3	41.4
IV	Total children of affected parents	4 [2]	5 [2]	9 [4]
	Affected children.....	3	2	5
	Per cent. of children affected....	75.0	40.0	55.6
V	Total children of affected parents	3 [1]	3 [1]
	Affected children.....	1	1
	Per cent. of children affected....	33.3	33.3
Total	Total children of affected parents	32 [7]	19 [6]	51 [13]
	Affected children.....	21	6	27
	Per cent. of children affected....	65.6	31.6	53.0



Familial angioneurotic edema.

The known portion of the history of angioneurotic edema in this family is shown in the form of a chart, in which the children of each family group are shown (from left to right in the order of their birth), while those affected and those who are supposed to have died of the disease are indicated by distinctive markings. It is believed to be complete and correct for all the groups that are shown. A glance at the chart will show one striking fact: that the line of inheritance of the disease has always been direct. It does not skip and reappear, but continues in an unbroken line from parent to child. There are only two instances where all the children of an affected parent have entirely escaped the angioneurotic trait, and there is no instance of a child of

22. Cassirer: Lewandowsky's Handbuch der Neurologie, 5, 256.

unaffected parents having exhibited the disease. This has not always been true of other angioneurotic families recorded in the literature; there have sometimes been skips and reappearance, but these are exceptions which are rarely noted; and direct descent is so constant as to suggest inheritance in the strict sense of a trait transmitted as a dominant characteristic under the mendelian law.

During many years the physical ills of all the members of this large family who resided in this community — and they include the majority of those shown in the chart — were looked after by Dr. J. R. Hinkle, a keen and able doctor of the old school, who, until his death some years ago at the age of 82, took great interest in their peculiar malady. After his death there were found among his effects some notes and letters concerning the family and their disease, from which many of the facts recorded in this history have been taken and which have added materially to its completeness.

Dr. Hinkle's experience with angioneurotic edema was unusual and extensive. It has probably come to few men to handle so large a group of related cases through so long a period of years; and his notes concerning it, while incomplete and often disconnected, are both interesting and instructive. His records bear no date, but were apparently prepared soon after 1890. While there is among them an entire absence of specific case histories or detailed clinical data, it is clear that he had studied his subject with much care, had gone thoroughly into the lineage of his cases, knew his patients well, and was conversant with the literature in existence at that time. The following quotations taken from his notes and letters give a better picture of the disease as it exists in the family under consideration than any that could be drawn from our own experience, and throw valuable side-lights on the clinical features of the disease. He says:

For thirty years I have had four or five families to wrestle with who have all of these years been subject to such attacks. . . . We have them to the fourth generation. Throughout these generations, as far as they take the type of the C. family, they expect to have the disease; as far as they take the type of the father or mother outside of the C. family they expect to be exempt. This is largely true. . . . The family throughout are remarkably exempt from organic diseases. . . . They are not subject to morbid blushing.

The area involved may be from a small spot in the skin to the area of the back, . . . a single joint of a finger or toe, . . . on any part of the surface a spot not larger than a silver fifty cent piece. . . . A hand or foot will suddenly become doubled in size. Where the surface is larger and furnishes more tissue, as in the femoral region, the back, or sides of body, suddenly there will be a great roll apparently as large as a man's arm thrust under the skin, extending from pelvis to axilla, neck, or shoulder. Again it is circular in form—6, 8, 10, or 12 inches in diameter. . . . The swelling does not follow the course of muscles or other tissues.

There is no part of the surface that I have not seen to suffer; also the tongue, larynx, lung, stomach, alimentary canal throughout. Every tissue except the bones and cerebrospinal axis may be involved. In one young lady, aged

18, the uterus in thirty minutes presented above the pelvis, as large and to the touch very much the appearance of a twenty-pound cannon ball. Pain was excruciating, not controlled by anodynes given heroically. In two and a half hours subsided, all quiet. . . . The heart is reported as having been involved. I have not seen such. An attack involving the heart would make short work of it. In such, death is immediate, hence a physician does not see them; nor is there any history except that they are dead. . . . In this community any statement as to the extent of the swollen condition of these people would not be classed as extravagant. To a stranger I do not know, hence I have not indulged in excess but have been moderate.

The swelling usually begins, or rather the first warning of the approach is in a small stinging sensation in the part attacked, described by the patient as the smallest possible point, but sharp and positive, probably the stretching of a single nerve capillary in the skin. Very soon this is multiplied and the tumor is perceptible. As the tumor increases in size the sharp pain does not increase in proportion to the increase of the tumor, but takes on a heavy feeling of compression, and motion in the part is obstructed. The skin becomes tense and shining, and distended often to the limit of its elasticity, the epidermis showing numerous cracks and fractures. . . . There is no capillary engorgement, no throbbing pain, no wall of lymph as in an inflammatory process.

Vasomotor constriction is apparent in all attacks. In the outset it is the best guide to prognosis. If in the beginning of the attack the superficial circulation is fairly maintained and the artery is not too much constricted, there is reason to expect a favorable result; if the reverse, and there is a sudden receding of surface manifestation of circulation with the artery materially constricted, there may be little tissue involved as yet but there will soon be an unpleasant abundance, with collapse to the limit of life. . . . When any considerable amount of tissue is involved the depression is great. . . . The family has long since learned to look to this feature. If for a day or two a member is uncomfortable, manifesting a disappearing superficial circulation, the radial artery becomes narrow and constricted, there is great anxiety. If a swelling does occur at this time it will probably be extravagant. If the swelling appears suddenly and circulation is fairly maintained, the prognosis is favorable even though a large amount of tissue be involved if no vital organ be a victim. . . . The disturbed circulation may be manifest and no active swelling. We have clouds when we have rain; may have clouds and no rain.

In the young and others who are vigorous the swelling is usually very prompt in appearance; that is, in thirty minutes to an hour it will often be fully developed. Again it will be twenty-four hours in attaining its full force. The promptly developing attacks usually recede as promptly. With age or an exhausted system the swelling is much slower in developing, is not so intense, and continues longer, may be two or three days. As the vitality wanes the swelling moderates and finally ceases to appear, but the patient passes through all the other conditions of an attack, but it is not localized but diffused through the system. When this condition prevails, it requires a week or two to pass through an attack. Finally there becomes a continuous chronic morbid state that does not manifest remissions and exacerbations. The transition from the acute to chronic form is not sudden, but may be years. Nor is this a new neurosis or another variety, but the same disease with an altered and lowered vitality.

In your report you indicate that the attacks cease to occur in many, but even if not it does not kill. In the people suffering so here my observation is that they all die directly or indirectly of the disease, either in the acute stage when a vital organ is invaded or in the chronic stage. As they grow older, or in the young who suffer frequently, they cease to have the local tumefaction, but instead there comes a chronic degenerative neurosis (this is not the right name, but I do not know a better one) with lack of assimilation,

waste of tissue, muscles weakened, moving sluggishly. When they attain to this stage they drag out a miserable, tedious, semipainful, inert existence and die sure.

COMMENT

The clinical characteristics of the swellings in these cases as described in the above quotations correspond in the main with the descriptions given by our patient of his own attacks and of the many he has observed among his relatives. We believe there can be no doubt of their essential correctness, however extravagant they may seem. We may well doubt, however, the correctness of Dr. Hinkle's conclusion that the deaths from chronic degenerative processes among those who have been afflicted are still deaths from the same neurosis which at other times produces only acute and transient swellings. The application of modern clinical and laboratory methods would probably give a better explanation for many of these. But the history of the occurrence of many deaths in the acute stages of the disease, from the swelling of vital organs, and especially of the throat, is so clear as to be beyond serious question.

We have spoken of angioneurotic edema as a disease. This may be objected to by those who hold it only a syndrome. It is indeed a symptom only, like a convulsion; but it is, on the other hand, a fairly distinct clinical entity, not a part of any general condition which we are able to classify with perfect confidence, and for practical clinical purposes may best be called a disease.

The etiology and pathogenesis of angioneurotic edema are obscure. In the particular group of cases with which this paper deals, it is clear that heredity is the chief etiologic factor; but beyond that we are scarcely able to go. Obscurity begins at once in attempting to do so, for we are not aware of either just what is inherited or what determines its manifestation in the form of local swellings.

There have, nevertheless, been numerous attempts to explain the disease. By one, the causative rôle has been ascribed to alcohol; by another, to malaria; by others, to various intoxications and infections; each basing his conclusion on a particular observation which seemed to support his theory. Practically all observers believe that it bears a close relation to many nervous conditions, both functional and organic. It is not infrequently associated with migrain, with epilepsy, with chorea, with neurasthenia, and it has been observed to accompany the lightning pains of tabes. It is most commonly found in neuropathic persons, and is often so closely bound up with other symptoms of neurosis that it almost loses its identity. Families in which the hereditary form appears are usually neuropathic families.

No age or sex or social condition shows a special predisposition. While the disease develops most frequently in the third and fourth

decades, no age is exempt. It has been seen in early infancy and in those past the eightieth year. Of 210 cases collected by Cassirer,²² 111 were males and 99 were females.

Sometimes the attacks repeat themselves with photographic correctness; sometimes they vary greatly. It has frequently been observed that one attack predisposes to others in the same locality — leaves some local sensitization which leads to future troubles. They may come once in a life-time, they may be repeated irregularly at intervals of years, or come on regularly or irregularly at intervals of months or weeks or days. And with all their repetition it may not be possible to find an exciting cause.

But it is sometimes otherwise. It has been frequently noted that small local traumas immediately precede the attacks. For instance, Halsted²³ saw an enormous swelling of the genitals develop immediately after a bicycle ride; and Courtades²⁴ saw the swelling develop after a blow in the eye of a boy aged 15 years, with recurrence thereafter in various parts of the body after any slight blow. Van Iterson²⁵ records a death from edema of the throat immediately following tonsillectomy, in which it was subsequently found that any small trauma was immediately followed by great local swelling. There are several cases like this in the literature. Three deaths in the family herein presented occurred from edema of the throat soon after the extraction of teeth. Thermic influences have often seemed to be the exciting cause, especially cold in many forms. Here probably belong those cases where the swelling comes only in the exposed parts of the body, as in the face and hands; and they constitute a large proportion of the whole number.

In other cases psychic influences seem to call forth the attack. The great emotions of fear and anger, or prolonged and arduous mental application have been observed immediately to precede the first attack. One of Cassirer's⁴ patients always got the swelling when he first saw it appear in his child; and he refers to a patient of Steckel who always developed an acute edema of the leg when crossing a certain place unless he was accompanied by his physician, when the swelling did not occur.

But these facts, if indeed they are facts, scarcely clarify the subject. They do not explain the pathogenesis of the chief symptom, which is edema. It would seem that there must be some irritant to the capillaries concerned, and that through it either the lymph secretion is

23. Halsted: *Am. Jour. Med. Sc.*, 1905, **128**, 863.

24. Courtades: Reference by Cassirer, Lewandowsky's *Handbuch der Neurologie*, **5**, 256.

25. Van Iterson: Reference by Cassirer, Lewandowsky's *Handbuch der Neurologie*, **5**, 256.

increased, or the vessel walls are so changed that they let through more transudate, or there is caused an increased absorptive power of the surrounding tissues. Experimental evidence of influence of this sort is not at hand, however, and we are left with only theories. Certain clinical observations, as urged by Cassirer and others, point strongly to the toxic, autotoxic, or infectious origin of certain cases. These come on acutely, recover, and do not recur except by repetition of the same toxemia. This group stands close to urticaria and purpura. On the other hand, the cases of direct or indirect heredity, in which the nervous conditions are predominant and which are related to other nervous affections, are apparently not dependent on outside influences. They regularly recur, and psychologic influences are etiologically important. But even here, it seems possible that through the influence of the nerves some toxic substance may be developed locally, causing temporary injury to the vessel walls or tissues; though wherein this supposed susceptibility of the nerves may lie is not known. In such cases we must deal with what appears to be an instability of the central nervous system, as in many other diseases, without positive knowledge of the nature of the defect.

A careful metabolic study of an angioneurotic woman, aged 54 years, was recently made by Miller and Pepper.²⁶ They found a slight increase of nitrogen retention during the attacks, and a reduced elimination of chlorids for three or four days preceding them, but no other changes. They believe that a low chlorid intake will have a beneficial effect on the attacks, but they do not find in their studies an adequate explanation of the cause. There is a tendency among some observers to find the glands of internal secretion at fault, but the relation is not made clear.

A point that seems not to have been considered sufficiently heretofore in this connection is that of specific or nonspecific protein sensitization after the manner of anaphylaxis. The history of idiosyncrasies in certain families, such as the tendency to hay fever and asthma, or the susceptibility to certain foods, has long been known. Similarly, a high degree of spontaneous sensitization to foreign proteins, specific or nonspecific in character and often multiple, with a distinct tendency for it to occur in families in which there is much evidence of inherited sensitization being transmitted as a dominant characteristic according to the mendelian law, has been recently pointed out by Longcope.²⁷ Herein may lie the explanation of angioneurotic edema. It offers the most fertile visible field for future investigation.

26. Miller and Pepper: *Metabolism Studies of Angioneurotic Edema*. THE ARCHIVES INT. MED., 1916, **18**, 551.

27. Longcope: *Am. Jour. Med. Sc.*, 1916. **152**, 625.

While the experimental study of immunity and anaphylaxis has seemed to establish the principle that transmission from mother to offspring, while it does occur, is in no sense a true inheritance, but is a passive transference of immune bodies to the child through the blood or milk of the mother and is very transient in character, Longcope has pointed out that the facts so far collected regarding the familial tendency of idiosyncrasy to foreign protein in man do not accord absolutely with those observed in experimental transference of immunity and anaphylaxis in animals. In the first place, sensitization in man is not transient, but often of years' duration; in the second place, it may continue through successive generations; and in the third place, it is often noticeable principally or solely in the male members. And finally, the sensitization may not always be to the same protein; in one family which Longcope studied the father was sensitive to horse serum and the son to egg-white. If inheritance is a factor, therefore, it cannot be simply by means of passive transfer from mother to offspring, but in some instances, at least, would seem to be a true inheritance of cell characteristics derived from one of the parents. In the important work recently published by Cooke and Vander Veer,²⁸ they have shown from a clinical study of the family history of 621 patients suffering from evidences of protein sensitization, chiefly hay-fever, that sensitization affects members of families in a proportion which closely approximates the theoretical figures of the mendelian law. They believe that the inheritance consists in the transmission of a tendency to sensitization only, or of a particular susceptibility, and not of the sensitizing substance itself. And they look on angioneurotic edema as a true anaphylactic reaction.

As to what may be the nature of the substances on which such a sensitization might depend in the case of angioneurotic edema we have no present knowledge, but it would seem that they necessarily must be common things and of general distribution, for in no other way can we account for the frequency and repetition of the attacks. Certain bacterial proteins might answer the requirements. It will be remembered that the original case of the disease in the family whose history has been presented was associated with an attack of quinsy. Is it possible that some sensitization to the products of the streptococcus could have arisen at that time which manifested itself later as a profound reaction to each mild flare-up of an infection which would ordinarily be harmless and pass unnoticed? And could the ubiquity of the streptococcus be responsible for keeping the sensitization active in particularly susceptible tissues? The suggestion is not made with confidence, but it may be worthy of consideration in future studies.

28. Cooke and Vander Veer: *Jour. Immunol.*, 1916, **1**, 201.

A discussion of the symptoms, diagnosis, prognosis and treatment of angioneurotic edema lies beyond our present purpose. The symptoms are almost wholly occasioned by the swelling and will differ according to its location. If in the skin, the large, pale, elastic and nonpitting swellings, which are nearly free from abnormal sensation, should be readily recognized. The attacks come on acutely and are usually unheralded. They last for a few hours to a few days and disappear quickly, leaving no trace of their former existence. If the air passages are attacked, grave symptoms of obstruction may occur, leading even to death; but it is said that death is practically unknown except in the familial cases. If internal organs are invaded there may be much pain, and differential diagnosis becomes important. Not a few laparotomies have been performed in the belief that there was intestinal obstruction, as in the report of Bogart,²⁹ or ruptured tubal pregnancy, as in a case reported by Briggs.³⁰ The history of previous local swellings, either in the person concerned or in other members of his family, is important in this relation.

Concerning treatment, it only needs to be said that our efforts are rarely effective. Only to a small extent can we limit the attack, and we cannot prevent recurrence.

29. Bogart: *Ann. Surg.*, 1915, **61**, 324.

30. Briggs: *Fulminating Pelvic-Abdominal Edema Simulating Ruptured Tubal Pregnancy*, *Jour. Am. Med. Assn.*, 1908, **50**, 528.

EXPERIMENTAL HYDRONEPHROSIS

FUNCTIONAL AND ANATOMIC CHANGES IN THE KIDNEY FOLLOWING PARTIAL URETERAL OBSTRUCTION *

N. M. KEITH, M.D., AND D. S. PULFORD, JR., M.D.
BALTIMORE

During the last fifty years many investigators have turned their attention to the study of the effect of increased intra-ureteral pressure on the kidney parenchyma. Much of the work has been carried on in an effort to ascertain the effect of ureteral ligation, with the result that the pathologic processes involved were found to follow a definite sequence. Then again, the relation of these pathologic lesions to renal function has been studied in various ways, usually on a single kidney with the opposite organ intact. With the introduction of newer methods for the study of renal function, particularly in the last fifteen years, we have thought it of interest to investigate the conditions brought about by subjecting a kidney to back pressure while it was still eliminating the waste products of metabolism.

By partially obstructing one ureter with a small rubber band and removing the opposite kidney, Keith and Snowden¹ demonstrated changes in renal function along with the development of hydronephrosis. Under these conditions the single kidney, subjected to increased intra-ureteral pressure, must necessarily carry on the total renal excretion. Functional changes were to be expected. Whether similar changes would be brought about by the partial occlusion of both ureters seemed to be a matter for investigation, since such a procedure would more closely resemble the effects produced by obstructions in the lower urinary tract that are so frequently observed clinically. The chief object of the investigation was to study functional changes that might occur from day to day in an animal when the only deviation from normal was an increased intra-ureteral pressure.

Two types of renal insufficiency were observed after partial occlusion of the ureters: first, an acute type with symptoms of severe renal insufficiency which soon resulted in death; second, a chronic condition in which the kidneys might show little or no functional change for a considerable period, but acute renal insufficiency and death occur later. In a few experiments, recovery of function was studied after the removal of its obstruction.

* Submitted for publication June 14, 1917.

* From the James Buchanan Brady Urological Institute and the Medical Clinic of the Johns Hopkins Hospital.

1. Keith, N. M., and Snowden, R. R.: Functional Changes in Experimental Hydronephrosis, *THE ARCHIVES INT. MED.*, 1915, **15**, 239.

METHOD OF PROCEDURE

As in the former experiments, female dogs were used exclusively because of the ease of catheterization. The animals were operated on under surgical aseptic technic. After entering the abdomen through a midline incision, the ureters were approached through the posterior peritoneum just below the lower fold of each kidney, and rubber bands placed about the ureters as described in the previous paper. In the former work the band was placed about the ureter just above its entrance into the bladder, but because of Lucas' observation² that the ureteral musculature in the middle third of the ureter is able to overcome considerable back pressure, it was thought more advisable to produce the partial obstruction as near as possible to the ureteropelvic junction. With the exception of two early experiments, this was the method adopted. In order to determine whether a method could be devised for accurately estimating the pressure exerted by the rubber band on the ureter, experiments were carried out on the cadaver with different mechanical devices. None of these was found to be satisfactory, so that in all of our animals the application of the bands to produce the required obstruction was purely a matter of practice and judgment at the time of operation. After the bands were in position the abdominal wall was closed and the animal returned to the metabolism cage. Previous to operation the dog was catheterized and the first twenty-four-hour specimen was collected from that time.

Control.—In order to be certain that the rubber band was entirely responsible for the increased intra-ureteral pressure, the following control experiment was carried out: The usual operation was performed on a small dog, D 17, and the bands were placed as loose loops about the ureters so that it was impossible for the rubber to exert any pressure on the ureteral wall. Functional studies were carried out on the fourth, fifth and seventh days and at weekly intervals until thirty-six days after operation, when the animal was sacrificed for anatomic study. During this entire period the functional tests were normal, the phenolsulphonephthalein output varying from 60 to 74 per cent. excretion in one hour after intravenous injection, the urea nitrogen of the blood from 7 to 11 mg., and at no time were albumin or casts present. The animal also retained its original weight.

Gross examination, at necropsy, revealed nothing abnormal in the ureters or kidneys. The elastic bands were surrounded as usual by connective tissue, but the ureter did not show any dilatation above the band. Histologically, the kidneys appeared normal.

This control experiment, together with others to be described later, is offered as evidence that, in order to produce ureteral obstruction by elastic bands, the latter must exert an actual pressure on the ureteral wall.

METHODS USED IN FUNCTIONAL STUDIES

The dogs were kept in metabolism cages and, as in our earlier experiments, were given a constant diet of 200 gm. of ground beef with 300 c.c. of water per day. This food was found to vary greatly in its nitrogen content, and, as daily analyses were not practicable, short experiments were done on starving dogs, which received a measured amount of water. In a certain number of animals, 200 c.c. of a 1 per cent. sodium chlorid solution, administered subcutaneously, made up the dog's daily allowance of salt and water.

2. Lucas, D. R.: Physiologic and Pharmacologic Studies of the Ureter, III, *Am. Jour. Physiol.*, 1908. 22, 245.

The use of female dogs made the urine collection by catheter at the beginning and end of twenty-four hour periods a fairly accurate procedure. Catheters were sterilized and the vagina given a liberal douche with sterile 4 per cent. boric acid solution in order to observe as nearly an aseptic technic as possible. When the phenolsulphonephthalein excretion was determined, only an aliquot portion of the urine containing the dye was used in its estimation, the rest being added to the twenty-four hour specimen. For the detection of albumin, heat and 5 per cent. acetic acid were used. A centrifuged specimen of urine was examined for the urinary sediment. The phenolsulphonephthalein test of Rowntree and Geraghty³ was employed according to their original technic. Both intravenous and intramuscular injections of the dye were used, as indicated in the protocols. Urine was collected by catheter and the bladder irrigated at the end of one or two hours, and the percentage of phenolsulphonephthalein determined colorimetrically. It is recognized that residual urine lying behind the ureteral obstruction would have a tendency to decrease the absolute amounts of phenolsulphonephthalein recovered within a definite time after injection. As the tests were carried out under like conditions of fluid intake, the error remains a constant one and changes in the amounts of the dye recovered from the bladder indicate corresponding changes in the amounts excreted by the kidneys. The total nitrogen in the urine was determined by the usual Kjeldahl and Gunning method, the urea as described by Marshall,⁴ and the ammonia by Folin's aeration method. In certain dogs creatin and creatinin of the urine were determined according to Folin.⁵ Duplicate determinations were always made. The nonprotein nitrogen of the blood was estimated according to the micromethod of Folin and Denis.⁶ This method was slightly modified, in that ethyl instead of methyl alcohol was used to remove the protein and the ammonia recovered after digestion by combined distillation and aeration. The Folin method⁷ for determining the creatin and creatinin in the blood was also employed, and the urea content of the blood was determined by Marshall's method.⁸ Estimations of the hydrogen-ion concentration of the blood in several dogs were carried out by the colorimetric method of Levy, Rowntree and Marriott.⁹ Gross anatomic specimens obtained at necropsy or in the case of one dog after unilateral nephrectomy, were preserved and prepared in Kaiserling's solution. Specimens for microscopic study were preserved in Zenker's fluid or 4 per cent. formaldehyd solution and sections were cut from paraffin blocks and stained with hematoxylin and eosin.

NORMAL LIMITS OF CONTROL STUDIES

All of the animals used in these experiments were subjected to several control tests before operation in order to eliminate as far as possible the presence of so-called "spontaneous nephritis." A cathe-

3. Rowntree, L. G., and Geraghty, J. T.: The Phthalein Test, *THE ARCHIVES INT. MED.*, 1912, **9**, 284.

4. Marshall, E. K.: A Rapid Clinical Method for the Estimation of Urea in the Urine, *Jour. Biol. Chem.*, 1913, **14**, 283.

5. Folin, Otto: On the Determination of Creatinin and Creatin in the Urine, *Jour. Biol. Chem.*, 1914, **17**, 469.

6. Folin, Otto and Denis, W.: New Methods for the Determination of Non-protein Nitrogen, Urea and Ammonia in Blood, *Jour. Biol. Chem.*, 1912, **11**, 527.

7. Folin, Otto: On the Determination of Creatinin and Creatin in Blood, Milk and Tissues, *Jour. Biol. Chem.*, 1914, **17**, 475.

8. Marshall, E. K.: A New Method for the Determination of Urea in Blood, *Jour. Biol. Chem.*, 1913, **15**, 487.

9. Levy, R. L., Rowntree, L. G., and Marriott, W. McKim.: A Simple Method for Determining Variations in the Hydrogen-Ion Concentration of the Blood, *THE ARCHIVES INT. MED.*, 1915, **16**, 389.

terized specimen of urine was found to be free from albumin, casts and blood cells. A phenolsulphonephthalein test was carried out, the injection being given either intramuscularly or intravenously and the output determined during a period of one or two hours. Thirteen animals, after intravenous administration, had an excretion varying from 52 per cent. to 83 per cent. in one hour; in six animals, after intramuscular injection, the excretion varied from 44 per cent. to 71 per cent. in one hour; and in four animals, from 63 per cent. to 70 per cent. in two hours. These figures compare closely with those given by Rowntree and Geraghty,⁸ with the exception of one animal, which excreted only 44 per cent. in an hour after intralumbar injection.

A determination of the urea nitrogen of the blood was also made before operation. The amounts obtained varied from 7 to 18 mg. per 100 c.c. These values bear a definite relationship to the amount and kind of food ingested, as Marshall and Rowntree¹⁰ have shown. The results obtained in the present experiments were on animals receiving a standard diet of raw beef or during a starvation period. In addition to the routine control determinations on all the animals, as outlined above, a number of special studies were carried out to determine normal values for certain other factors which are known to be disturbed in renal disease.

The total nonprotein nitrogen of the blood was determined in a series of nine normal animals and was found to vary from 22 to 34 mg. per 100 c.c. The animals were either receiving a standard ration of raw beef or were fasting. Pepper and Austin¹¹ have shown variations in the blood nitrogen in dogs due to the ingestion of large amounts of protein food. The preformed creatinin nitrogen of the blood was estimated on several different occasions in six control starving dogs and was found to be from 0.17 to 0.44 mg. per 100 c.c. Control determinations of the creatin nitrogen in three normal dogs varied from 1.4 to 1.8 mg. The hydrogen-ion concentration of the blood was not determined prior to operation. Levy, Rowntree and Marriott's⁹ figures for two normal dogs were: serum P_H 7.7 and 7.75 and whole blood (oxalated) 7.55 and 7.6. Marshall and Rowntree¹⁰ in their paper on experimental phosphorus and chloroform poisoning give normal figures for the whole blood as P_H 7.55 to 7.70.

Four animals were studied for control values in regard to the excretion of nitrogen in the urine under starving conditions. The total output of nitrogen varied considerably, but the percentage content of

10. Marshall, E. K., and Rowntree, L. G.: Studies in Liver and Renal Function in Experimental Phosphorus and Chloroform Poisoning, *Jour. Exper. Med.*, 1915, **22**, 333.

11. Pepper, O. H. P., and Austin, J. Harold: Experimental Studies of Urine and Blood Nitrogen Curves After Feeding, *Jour. Biol. Chem.*, 1915, **22**, 81.

the different constituents studied remained fairly constant. The urea nitrogen made up from 71 to 83 per cent. of the total nitrogen, ammonia nitrogen from 3.4 to 7.4 per cent., preformed creatinin nitrogen from 2.6 to 4.4 per cent. Table 1 gives the findings in one of these normal starving dogs, together with the partition of the non-protein nitrogen in the blood.

The figures for the urea nitrogen percentage in the urine are lower than those reported by Howe, Mattill and Hawk¹² in starving dogs, but compare closely with those of Underhill and Kleiner.¹³

TABLE 1.—NITROGEN PARTITION—CONTROL, DOG 26.

Day	Weight. Kg.	H ₂ O Intake, C.c.	Blood			Urine							
			Total Nonpro- tein N, Mg. per 100 C.c.	Urea N, Mg. per 100 C.c.	Creat- inin N, Mg. per 100 C.c.	Amt., C.c.	Total N, Gm.	Urea N, Gm.	NH ₃ N, Gm.	Creat- inin N, Gm.	Urea N, per Cent.	NH ₃ N, per Cent.	Creat- inin N, per Cent.
1*	16.0	300	..	18	150	6.08	4.76	78
3	200	..	12	135	4.08	3.42	0.302	83	7.1	...
4	15.5	300	29	14	0.28	230	8.93	7.08	0.550	0.83	79	6.0	3.7
5	15.0	300	..	15	170	6.05	4.49	0.24	74	...	4.0
6	155	..	11	140	4.54	3.46	0.17	76	...	3.9
7	15.1	60	34	11	0.44	120	4.24	3.02	0.265	0.18	73	6.0	4.3

* Phthalein excretion 44 per cent. Urine negative for albumin and casts. Urine acid to litmus during whole period.

There is a considerable variation in the total amount of urine excreted by a starving animal under constant fluid intake. This variation seemed more marked when the water was taken by mouth. In order to make the liquid intake more constant and permit studies in chlorid retention, 1 per cent. sodium chlorid solution (200 c.c.) was introduced subcutaneously in five normal animals. Using this method, the daily variations in the urine volume of the individual animals seemed more constant than when water was taken by mouth.

TYPES OF RENAL INSUFFICIENCY RESULTING FROM INCREASED BACK PRESSURE

From the beginning of these experiments it was found impossible at the time of operation to determine the extent of the back pressure and renal involvement that would result from the partial ureteral obstruction. As previously stated, no satisfactory method was found

12. Howe, Mattill and Hawk: Distribution of Nitrogen During a Fast of One Hundred and Seventeen Days, *Jour. Biol. Chem.*, 1912, **11**, 103.

13. Underhill, Frank P., and Kleiner, Israel S.: Further Experiments on the Mechanism of Salt Glycosuria, *Jour. Biol. Chem.*, 1908, **4**, 165.

to be available for estimating the tension exerted by the rubber band on the ureteral wall. With increasing experience we were able to place the bands so that in all the animals an increased intra-ureteral pressure followed the operation, but subsequent functional studies revealed wide variations as to the actual renal damage. Necropsy findings also differed in the type and extent of the kidney lesions. As the work progressed functional and anatomic findings became less bizarre and the differentiation into two distinct types became possible.

In the first place, one group of animals quickly developed signs and symptoms of severe renal involvement following the insertion of tight rubber bands. Urine was passed, the volume being sometimes actually more than normal, though usually less. Functional studies showed a rapid progressive accumulation in the blood of substances normally excreted, and within a week the animal died of acute renal insufficiency. In a second group of animals, a condition of chronic renal impairment gradually developed after varying lengths of time. One series of dogs in this group showed mild functional and pathologic changes soon after operation, followed by apparent recovery, but later a chronic condition developed. Another series gave no evidence of such early changes, but subsequently manifestations of a chronic lesion appeared. Several animals lived for periods of weeks and months in good general health with the functional findings indicating chronic lesions. Finally, symptoms of acute renal insufficiency developed rather suddenly, and within a short time the animal succumbed.

Group 1.—Acute type: Aside from the fact that urine was being passed, the symptoms resembled closely those resulting from double ureteral ligation. Vomiting began a day or two after operation and subsequently neither food nor water could be retained. The dogs became much less lively and gradually weakened. No convulsive movements were observed and the dogs seemed mentally alert until death.

Three animals of this type were studied from a functional standpoint. Dog 21 from the fourth day was able to excrete only a trace of phenolsulphonaphthalein and the urea nitrogen of the blood reached 116 mg. per 100 c.c. on the sixth day. The dog was found dead on the eighth day following operation. Necropsy showed both kidneys enlarged and engorged, the ureters and pelves distended above the constriction caused by the bands. On section, the pelves were dilated, the left to a greater degree than the right, and both contained a pus-like exudate. The cortex was thicker than normal and edematous. All the organs were soft and edematous from postmortem change, but no gross lesions were observed except in the kidneys. Histologic sections were not made because of the marked postmortem change.

The second animal, Dog 5, presented a similar picture, and on the fifth day the bands were removed following double lumbodorsal incision. A large amount of urine was secreted on the two subsequent days, containing a daily output of nitrogen of 4 gm., but renal function, as shown by the phenolsulphonephthalein test and the urea nitrogen of the blood, did not improve. The dog was found dead on the eighth day after partial obstruction and three days after the removal of the bands. (See Table 2.) Necropsy revealed an early peritonitis on two to three loops of bowel, although the remaining viscera and the entire parietal peritoneum were smooth and glistening and the abdominal cavity contained no free fluid. The organs were negative, with the exception of the kidneys. These were both enlarged and the capsular veins distended. The ureters and pelves were dilated and contained mucopurulent material.

TABLE 2.—EFFECTS OF PARTIAL OBSTRUCTION OF URETERS IN DOGS
Dog 5, Weight 11.7 Kg.

Date	Day of Operation	Intake Water, C.c.	Urea N Blood, Mg. per 100 C.c.	Urine							
				Amt., C.c.	Specific Gravity	Reaction to Litmus	Albumin	Total N, Gm.	Urea N, Gm.	Urea N, per Cent.	Phthal. cin, per Cent. in 2 Hrs.
10/ 6	...	200	11	Neg.	55-1 hr.
10/ 9	1
10/12	4	300	80	Trace	20
10/13	5	100	64	2	0
10/13	3:30*	3
10/14	6	250 Saline intrav.	73	594†	1.015	Acid	Trace	4.14	3.21	77	33
10/15	7	0	111	613	1.012	Acid	Trace	3.91	2.35	60	4
10/16	8‡

* Bands removed. No food given on days tabulated.

† Urine and vomitus in seventeen hours.

‡ Dog found dead.

Histology.—Both kidneys showed extensive polymorphonuclear infiltration and edema; in the left the changes were more advanced, with necrosis and abscess formation. No connective tissue changes were observed. The tubular epithelium was markedly degenerated, due, partially at least, to postmortem change. The tubules contained hyaline, granular and pus casts.

The third animal, Dog 4, was observed from the standpoint of nitrogen metabolism before and after operation. The dog was found dead on the fifth day, and at necropsy the kidney lesions were similar to those in the two previous experiments. The studies in regard to

some of the nitrogenous constituents of the blood and urine before and after operation are summarized in Table 3. Between the second and third days it will be noted that with a marked rise in the nitrogen in the blood the excretion in the urine was increased. The percentage relation of urea, ammonia and creatinin nitrogen in the urine remained practically normal. On the fourth day it is to be noted that the creatinin nitrogen of the blood was 0.54 mg., a figure considerably higher than the normal value, while the total nonprotein nitrogen was 183 mg., or four times the upper limit of normal. This great increase in total nitrogen was due chiefly to the high percentage (75 per cent.) of urea.

The results of these experiments indicate changes that are typical of a rapid progressive renal lesion. Elimination by the kidney ceases within a few days and the animal quickly succumbs.

TABLE 3.—NITROGENOUS CONSTITUENTS OF BLOOD—
Dog 4

Date	Day of Operation	Condition	Weight, Kg.	Intake Water, C.c.	Blood		
					Total Nonprotein N, Mg. per 100 C.c.	Urea N, Mg. per 100 C.c.	Creatinin N, Mg. per 100 C.c.
2/14	...	Good.....	9.22	125	27 [*]	8	0.17
5/15	...	Good.....	8.96	300	22	10	0.18
5/15	1	Operation					
5/16	2	Good.....	8.59	0	...	31
5/17	3	Signs of distemper.....	8.24	200	157	110
5/18	4	Signs of distemper.....	7.72	300	183	138	0.54
5/19	5	Found dead					

* Twenty-one hours after operation.
† Urine contained watery vomitus; 35 c.c. obtained by catheter; 570 c.c. in cage bottle.

Group 2.—The second group of animals gradually developed chronic renal lesions. In one series early changes were present, while in the second little or no evidence of early functional impairment could be demonstrated, but subsequently manifestations of a chronic condition appeared.

Functional and pathologic changes of a mild degree were observed during the first week in three animals in this group. The phenolsulphonephthalein output was moderately diminished, the urine contained a trace of albumin and in one experiment (Dog 16) the urea nitrogen in the blood amounted to 26 mg. per 100 c.c., a figure slightly above normal. Detailed functional findings in Dog 2 are shown in Table 4. Dogs 2 and 3 were sacrificed on the seventh and eighth days to determine the extent of the pathologic process. It is of interest that almost

identical lesions were found in the two animals. The pelves and ureters were only slightly dilated, the kidneys normal in size, with slight engorgement of the capsular veins. On histologic examination the abnormal findings were, slight dilatation of the tubular lumina, congestion and polymorphonuclear infiltration of the pelvic mucosa and papillae, with slight, if any, alterations in the tubular cells. The glomeruli appeared normal in every respect.

The third animal, Dog 16, was observed for a period of twenty-one days, and during this time the phenolsulphonephthalein output varied from 25 to 54 per cent. in two hours, the urea nitrogen of the blood on one occasion, the fourth day, reached 26 mg. to 100 c.c., while during the remainder of the experiment the amount varied between 11 and 14 mg. Pus cells continued to be present in the urine, which was

—AND URINE BEFORE AND AFTER OPERATION

Dog 4

Urine											
Amount in 24 Hrs.	Specific Gravity	Reac- tion to Litmus	Total N, Gm.	Urea N, Gm.	Urea N, per Cent.	Creat- inin N, Gm.	Creat- inin N, per Cent	NH ₃ N, Gm.	NH ₃ N, per Cent.	Albu- min	Sedi- ment
112	1.040	Acid	3.4	2.58	76.0	0.113	3.3	0.198	5.5	Neg.	Neg.
90*	1.035	Acid	1.63	1.16	71.4	0.058	3.5	0.055	3.4	Neg.	Neg.
170	1.028	Acid	2.31	1.72	74.6	0.062	2.6	0.116	5.0	Neg.	Neg.
35†	1.022	Acid	Pos.	

increased in amount and of a low specific gravity. The animal was sacrificed at the end of three weeks because of an accidental perforation during catheterization. The necropsy findings were similar to those of Dog 2 and Dog 3, except that throughout the entire parenchyma of the right kidney there was a profuse purulent infiltration. Gross specimen is shown in Figure 1.

From these experiments it would seem that a low grade ureteral obstruction may give rise to early mild functional disturbances. The stages in the transition from this early mild reaction to a chronic type of lesion are outlined in the following protocol:

Dog 9.—Small, long-haired fox terrier, weighing 6.1 kg. Operation Nov. 20, 1915. Bands were placed about both ureters below the lower poles of the kidneys. Recovery was excellent.

Nov. 22-27, 1915. The functional changes were similar to those observed in Dog 16. Urea nitrogen in the blood reached 32 mg., the phenolsulphone-

phthalein excretion was as low as 30 per cent. in one hour after intravenous administration; the urine volume was increased to 250 to 280 c.c. and was of a low specific gravity (1.020). A trace of albumin was present and isolated leukocytes, but no casts.

Nov. 29, 1915. Phenolsulphonephthalein excretion and urea nitrogen of the blood were normal. From the thirteenth to the twentieth day the dog suffered from a mild attack of distemper without any apparent effect on renal function.

Dec. 15, 1915. Weight 6 kg. Blood urea nitrogen, 12 mg. per 100 c.c. Phenolsulphonephthalein 50 per cent. in one hour. The general condition of the dog was excellent. During the next three weeks no studies as to function were carried out because of the splendid condition of the animal.

Jan. 6, 1916. Forty-eighth day: urea nitrogen of the blood, 11 mg. Phenolsulphonephthalein, 7 per cent.

Jan. 21, 1916. Since January 6 the phenolsulphonephthalein output has been extremely low, 3 to 7 per cent. in one hour, but associated with a normal urea nitrogen content of the blood. The dog appears to be in good health.

TABLE 4.—DATA OF EXPERIMENT ON DOG 2

Dog 2. Weight 8.3 Kg.

Date	Day	Condition	Intake		Blood Urea N, Mg. to 100 C.c.	Urine					Phthal-ein, 2 Hrs.
			Meat, Gm.	Water, C.c.		Amount, C.c.	Specific Gravity	Reac-tion	Albu-min	Sedi-ment	
10/20											
10/22	1	Operation	200	200	9	...	1.015	Acid	Neg.	Neg.	53*
10/25	4	Good	300	16	...	1.026	Acid	V. Sl. Tr.	30
10/26	5	Good	120	300	15	200	1.020	Acid	Trace	W.B.C. Bact.	32
10/27	6	Good	140	300	13	230	1.023				
10/28	7	Good	200	300	9	162	1.023				
10/29	8	Sacrificed	200	300	12	316	1.019	Acid	Plus	W.B.C.	71

* One hour intramuscularly.

April 12, 1916. Since January 21 the dog has been in excellent general condition. The urea nitrogen of the blood varied from 11 to 28 mg. per 100 c.c.; the creatinin nitrogen of the blood remained stationary at 0.50 mg. per 100 c.c. while the phenolsulphonephthalein excretion ranged from 5 to 28 per cent. in one hour. On four occasions during this period the animal's intake was limited to a daily subcutaneous injection of 200 c.c. of a 1 per cent. sodium chlorid solution, the experiment extending over three to four days. With this intake the urine volume was large, 200 to 250 c.c.; the specific gravity remained rather low, 1.018 to 1.027, and the total output of urea nitrogen was remarkably constant in amount from day to day, amounting to 1 to 1.5 gm. A small quantity of albumin and pus cells were constantly present.

April 13, 1916. The rubber bands were removed from both ureters through dorsal lumbar incisions to ascertain the effect on renal function.

April 14, 1916. The dog recovered well from the operation. Nothing was given by mouth in the last twenty-two hours; 200 c.c. of 1 per cent. sodium chlorid were injected subcutaneously. The output of urine was 100 c.c.; phenolsulphonephthalein, 12 per cent. in one hour; total nonprotein nitrogen of blood, 36 mg., a similar amount to that obtained just before operation.

April 22, 1916. The general condition of the dog was excellent. Nothing was given by mouth for the previous three days. Two hundred c.c. 1 per

cent. sodium chlorid solution were given subcutaneously daily. The urine output was 190 to 200 c.c.; specific gravity 1.017 to 1.020; and the total nitrogen 0.95 to 1.53 gm. Phenolsulphonephthalein, 28 per cent. Blood: total nonprotein nitrogen, 32 to 34 mg., preformed creatinin nitrogen, 0.51 mg.; creatinin nitrogen, 2.4 mg. The arterial blood pressure, taken directly in the femoral artery, at 11:45 a. m. was 125 mm. Hg; 12 noon, 150 mm. Hg. The dog was sacrificed with ether for anatomic study. Figure 2 shows the gross anatomic picture.

In this experiment, extending over a period of several months, the essential facts can be summarized as follows: After early functional changes in the first ten days, normal function was present at the end of one month. From that date until the conclusion of the experiment renal function was impaired—the amount of insufficiency varying from

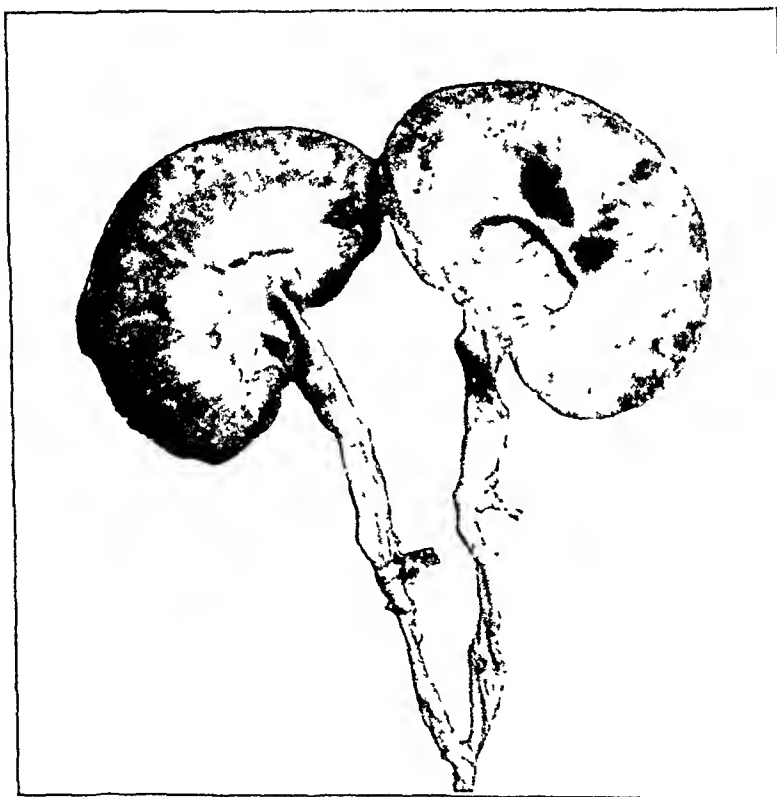


Fig. 1.—Kidneys of Dog 16, showing effect of low grade ureteral obstruction.

time to time — yet the general health of the dog remained constantly good. Numerous observations showed normal concentrations of blood urea associated with extremely low phenolsulphonephthalein elimination.

In the four previous experiments the early renal changes resulting from partial ureteral obstruction were emphasized. Experiments on three additional animals clearly indicate that early functional disturbances may be practically absent and yet damage to the kidney occur. In Dog 8 (Table 5) a trace of albumin was the only evidence of renal involvement, and yet marked insufficiency subsequently developed. Disturbed function was not suspected until the fifty-fifth day, when

the dog for the first time refused to take food. The phenolsulphonophthalein excretion was then only 3 per cent. in one hour, and the urea nitrogen of the blood 66 mg. per 100 c.c. Subsequent studies showed no signs of improvement and the animal was found dead ten days later. Necropsy revealed two large sac-like kidneys, the right much larger than the left (Fig. 3). Histologically, the chief findings were diffuse connective tissue infiltration, degeneration of the tubular epithelium and the absence in either kidney of any acute inflammatory reaction.

The clinical course of Dog 10 was similar to that in the foregoing experiment. In both animals the urea nitrogen in the blood was well within the normal limits on the sixth day, but in Dog 8, 62 per cent.

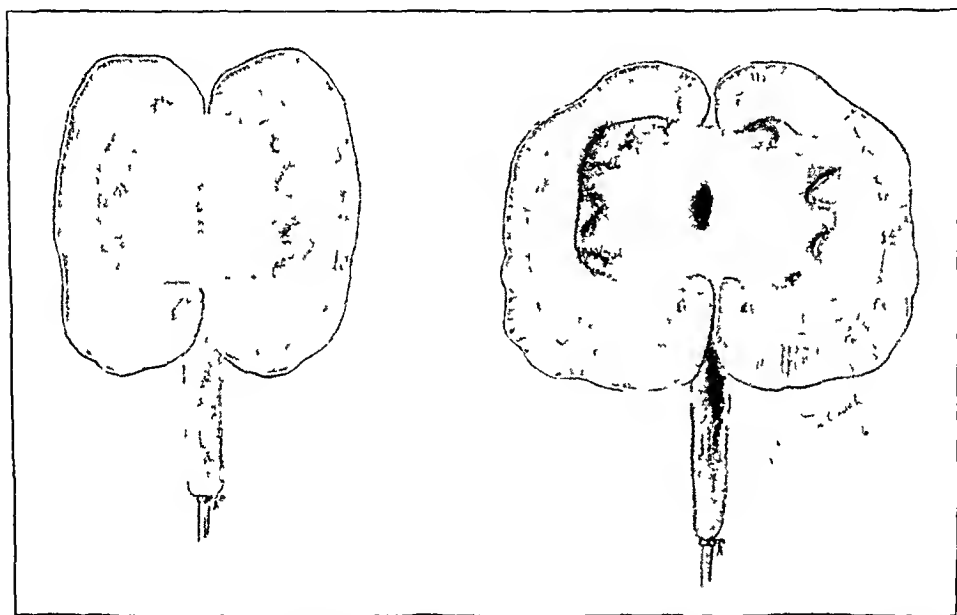


Fig. 2.—Kidneys of Dog 9. Kidney function impaired by prolonged partial ureteral obstruction.

phenolsulphonophthalein was excreted in one hour, while only 32 per cent. was passed by Dog 10 in two hours. Both animals subsequently presented symptoms of marked renal insufficiency at approximately the same time, the forty-ninth to fifty-fifth day, and from that time on the phenolsulphonophthalein output was almost negligible. Another experiment yielded similar results (Dog 1). It is also worthy of note that the pathologic findings were similar in all three animals of this series, Dogs 1, 8 and 10.

The nitrogen metabolism was studied with special reference to the creatinin and creatin of the blood and urine during the acute terminal period in Dog 10, which is characteristic of the animals of this group. (Table 6. Gross specimens are shown in Figure 4.)

TABLE 5.—DATA OF EXPERIMENT ON DOG 8

Dog 8. Weight 7.2 Kg.

Date	Day	Condition	Intake Water, C.c.	Blood Urea N., Mg. in 100 C.c.	Urine				
					Amount, C.c.	Specific Gravity	Albu- min	Sed- iment	Phthal- cin, 1 Hr.
1915 11/18	1	Oper.	300	11	Neg.	Neg.	77
11/16	4	Good	300	22	.				
11/17	5	Good	300	16	...	1.036	F. Tr.	Neg.	
11/18	6	Good	300	13	62
11/23	11	Good	300	16					
1916 1/ 6	55	Sick	300	66	F. Tr.	Hyaline and gran- casts; pus cells	3
1/ 8	57	Sick	300	48	3
1/12	61	Sick	300	..	140	1.016	Plus	Hyaline and gran- casts; pus cells	
1/17	66	Found dead							

No food was given on days tabulated.

In Table 6, covering a period of nine days, the most noticeable fact is the remarkably constant output of total nitrogen in the urine, in spite of the fact that the urea nitrogen in the blood gradually rose from 103 to 167 mg. Similarly, the creatinin and creatin excretion during this period remained constant while the content of these substances in the blood gradually increased, creatinin nitrogen from 1 to 2.6 mg., creatin nitrogen from 3 to 5.9 mg. These results indicate the difficulties in attempting to demonstrate nitrogen retention in the body simply from quantitative estimations of the intake by mouth and output in the urine, and to emphasize the importance of blood studies in detecting renal insufficiency. It will be noted in this experiment as in Dog 4, that the urea nitrogen in the blood is a much higher figure in comparison to the normal than the creatinin nitrogen figure. On June 2, the urea nitrogen was five times greater than the upper limit of the values found in normal controls, while the creatinin nitrogen was about double that of the controls. This fact has been pointed out in clinical cases of severe nephritis by Folin and Denis¹⁴ and Myers and Lough.¹⁵ Observations of the hydrogen-ion concentration in the blood were made on two occasions during this terminal period in Dog 10.

14. Folin, Otto, and Denis, W.: On the Creatinin and Creatin Content of the Blood, *Jour. Biol. Chem.*, 1914, **17**, 487.

15. Myers, Victor C., and Lough, Walter G.: The Creatinin of the Blood in Nephritis. Its Diagnostic Value. *THE ARCHIVES INT. MED.*, 1915, **16**, 536.

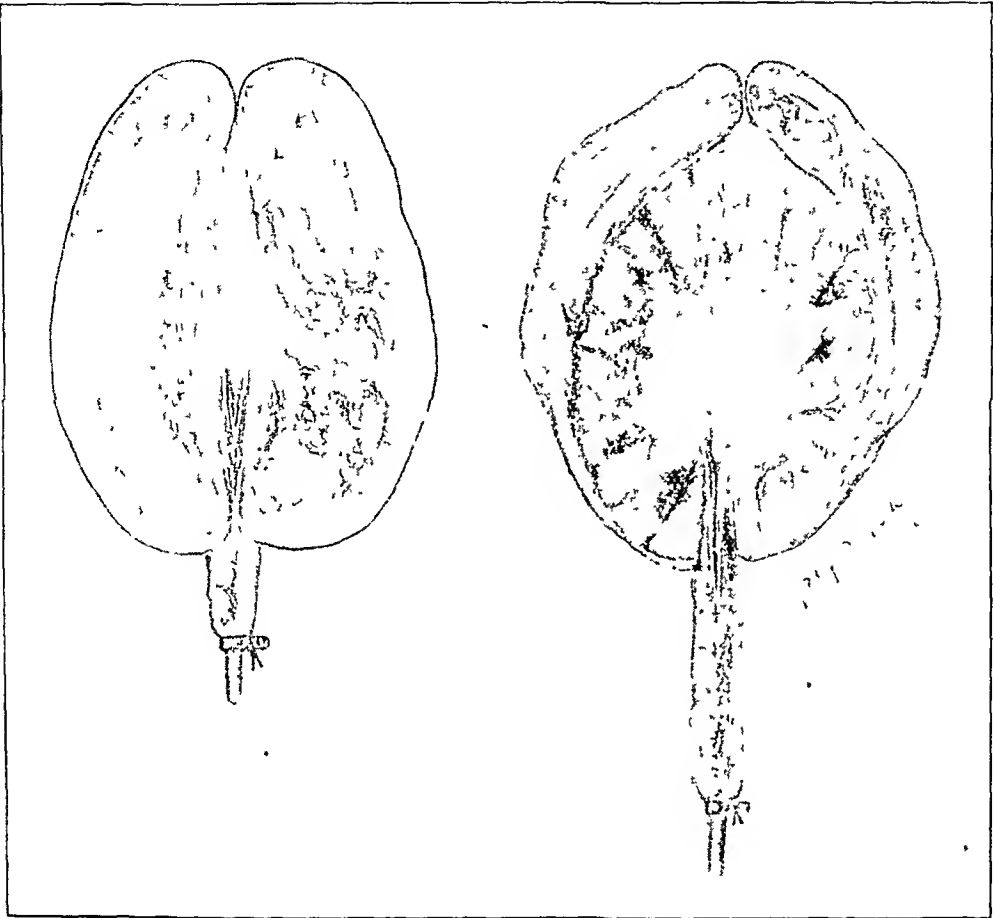


Fig. 3.—Kidneys of Dog 8. Severe damage to the kidney from prolonged partial ureteral obstruction.

TABLE 6.—DATA OF EXPERIMENT ON DOG 10

Dog 10. Weight 9.58 Kg.

Date	Blood				Urine		
	Total Non-protein N, Mg.	Urea N, Mg.	Creatinin N, Mg.	Creatin N, Mg.	Total Nitrogen, Gm.	Creatinin N, Gm.	Creatin N, Gm.
6/ 2*	145†	103	1.0	...	1.40	0.065	0.039
6/ 3	150	107	1.0	3.0	0.93	0.039	
6/ 4	...	108	1.3	...	1.11	0 057	
6/ 5	...	113	1.3	5.2	1.60	0.053	0.035
6/ 6	...	116	1.60		
6/ 7	...	147	1.84		
6/ 9	...	135	2.7	...	1.66	0 052	
6/10	...	143	2.6	5.9	2.05	0 059	0.033
6/11	...	167	2.4	4.8	1.17		

* Fifty-fourth day after operation.

† During the experiment the daily intake of water was 200 c.c. No food was taken.

That found on June 6 was normal, but the value for blood serum, P_{H} 7.2, recorded on June 3 (fifty-fifth day), was definitely more acid than normal. This finding corresponds with the hydrogen-ion concentration sometimes present in severe clinical cases of chronic nephritis.⁹

In the experiments just outlined, little evidence of renal insufficiency was observed until the sudden onset of the acute terminal condition. In order to follow more closely the development of the progressive renal lesion occasional studies were made on another animal over a period of five months. Striking variations in function were observed.

Dog 12.—Female, brown striped mongrel terrier, weighing 8.2 kg.
Dec. 2, 1914. Routine operation; bands were placed about both ureters.

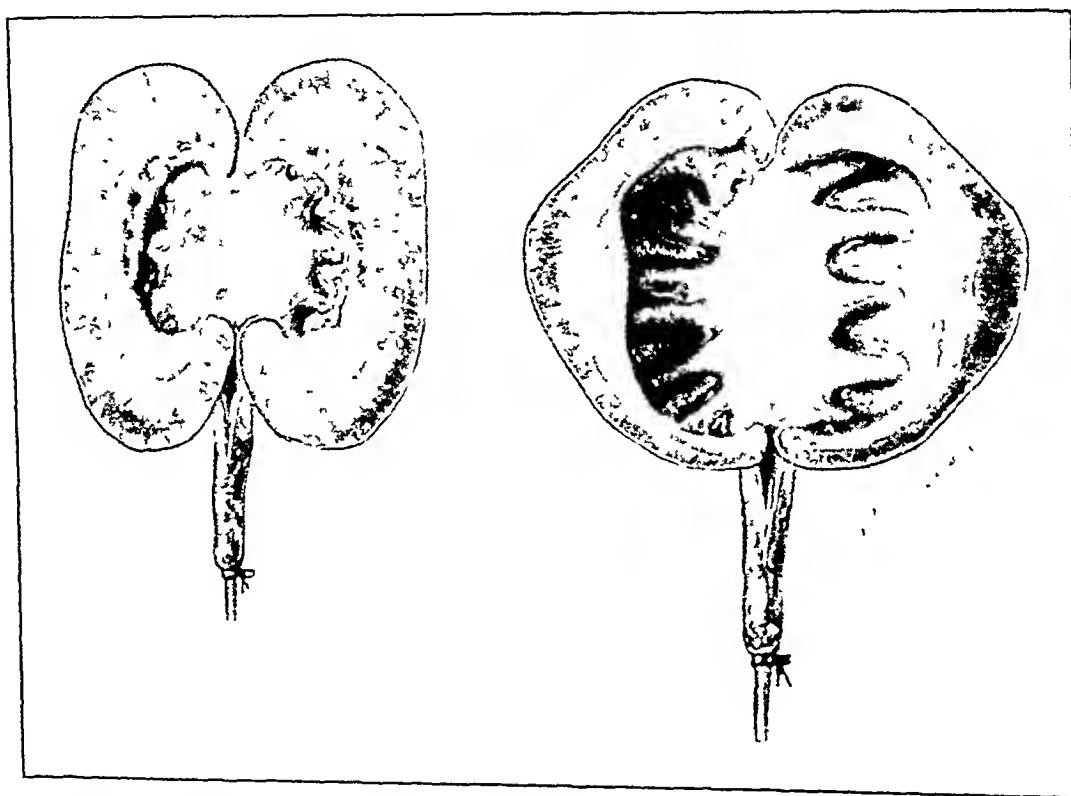


Fig. 4.—Kidneys of Dog 10. Severe damage to the kidney from prolonged partial ureteral obstruction.

Dec. 9, 1914. The general condition has been good since the operation. The animal takes food well. Phenolsulphonephthalein excretion, 40 per cent. in two hours. Urea nitrogen in the blood, 16 mg.

Dec. 16, 1914. Phenolsulphonephthalein, 22 per cent. in two hours. Urea nitrogen of the blood, 47 mg. Thus, on the thirteenth day after operation, renal function is definitely impaired. The urine shows traces of albumin and clumps of pus cells.

Dec. 17, 1914. Phenolsulphonephthalein, 30 per cent. Total nonprotein nitrogen of the blood, 50 mg. Urea nitrogen, 19 mg. Function has improved definitely in twenty-four hours.

Dec. 21, 1914. The dog has signs of mild distemper but in spite of this fact renal excretion is remarkably good. Phenolsulphonephthalein, 53 per cent. Urea nitrogen of the blood, 41 mg. A twenty-four-hour specimen of urine yielded 185 c.c.; specific gravity, 1.030.

Jan. 4, 1915. Signs of distemper have disappeared; the general condition is excellent. Total nonprotein nitrogen of the blood, 30 mg.; urea nitrogen, 23 mg. Hydrogen-ion concentration of the blood plasma (P_H) 7.6, normal figure. Phenolsulphonephthalein excretion, 28 per cent.

Jan. 18, 1915. Fiftieth day since operation. The dog appears healthy and aside from urinary findings and functional studies would be considered normal. Weight is 8.5 kg. Phenolsulphonephthalein, 35 per cent. Total nonprotein nitrogen in the blood, 47 mg. Urea nitrogen, 21 mg.

Feb. 6, 1915. Sixty-seventh day. Phenolsulphonephthalein, 27 per cent. Total nonprotein nitrogen in the blood, 36 mg.; urea nitrogen, 19 mg. General condition is unchanged.

Feb. 9, 1915. Seventieth day. Blood pressure, determined directly in the femoral artery; at 3:30 p. m., 150 mm. Hg, and at 4:00 p. m., 155 mm. Hg.

March 13, 1915. One hundred and second day. The general condition is excellent. Urea nitrogen in the blood, 35 mg. Phenolsulphonephthalein, 10 per cent. Volume of urine, 300 c.c.

April 10, 1915. One hundred and thirtieth day. Weight, 8.6 kg. Urea nitrogen of the blood, 18 mg. Phenolsulphonephthalein, 33 per cent.

May 7, 1915. One hundred and fifty-seventh day. Weight, 6.8 kg. The dog for the last few days seems sick, refused food and occasionally vomited. No muscular twitchings or convulsions were observed. The total nonprotein nitrogen in the blood was 84 mg.; urea nitrogen, 55 mg.; phenolsulphonephthalein, 4 per cent. in two hours.

May 16, 1915. One hundred and sixty-sixth day since operation. The dog was found dead.

Necropsy.—No abnormalities are apparent except in the urinary tract. For gross appearance of the kidneys see Figure 5. Both ureters are markedly dilated above the bands, the right more so than the left, with very thin sac-like walls. Both lumina are pervious to fluid under pressure. The left kidney is slightly larger than normal and on section the pelvis is moderately dilated, but the cortex and medulla can be distinctly differentiated. The right kidney is small and atrophied, the dilated pelvis being large in proportion to the kidney substance. Histologically the right kidney is composed almost entirely of scar tissue, while the left, aside from moderate scar tissue infiltration, shows definite changes in the tubular epithelium. There is no outspoken acute inflammatory infiltration in either organ.

The experiment with this animal is of interest for a number of reasons: (1) the length of life—over five months from the onset of renal insufficiency; (2) the apparent good health during this period; (3) the constant excretion of a large amount of urine of low specific gravity, containing pus cells; (4) the marked fluctuation in function as shown by the phenolsulphonephthalein excretion and nitrogen content of the blood; (5) the rapid terminal process, accompanied by symptoms and functional changes indicating a severe nephritis. The phenolsulphonephthalein excretion during the first four months was between 20 per cent. and 62 per cent. in two hours (intramuscular injection), the average output for fifteen determinations being 33 per cent. The total nonprotein nitrogen of the blood during the same period varied from 30 to 61 mg. The highest figure, 61 mg., is only a moderate rise above the upper limits of normal. The average of twelve estimations was 45 mg. On the other hand, the urea nitrogen of the blood showed more marked fluctuation; nineteen estimations were

made in all, the values varying from 10 to 47 mg., the average being 26 mg. This latter value is distinctly above that found under similar dietary conditions in the control dogs.

The termination of this chronic type of renal lesion is characteristic, in that kidney function as a whole rather suddenly collapses, serious symptoms develop and death ensues. A similar terminal condition occurred after a much shorter period in animals with only one kidney and that subjected to back pressure, as pointed out by Keith and Snowden.¹

THE EFFECT OF REMOVAL OF URETERAL OBSTRUCTION ON THE KIDNEY

The preceding experiments on eleven animals demonstrated that partial ureteral obstruction always produced anatomic changes in the ureter, renal pelvis and kidney parenchyma, associated with more or less impairment of renal function. The removal of the bands, therefore, offers a method for the study of a renal lesion following the withdrawal of the original etiologic factor. The experimental plan adopted was as follows: The animal was operated on in the usual way, the bands being put in place through an abdominal incision. Functional studies were then carried out daily, and when the phenolsulphonephthalein output and urea nitrogen content of the blood indicated renal impairment a second operation was performed. At this time dorso-lumbar incisions were made in the region of both kidneys, the ureters approached extraperitoneally and the bands removed. At the end of the next twenty-four hours the urine was collected and functional studies carried on as in the previous experiments. The period of starvation was usually continued for the next week so that the experimental conditions begun before the production of the original lesion were kept constant. The dogs were then allowed food and within a short time always appeared in good general condition. Five of these animals were observed for periods varying from twenty-two to 120 days after removal of the bands. The following protocol of the first experiment is given in detail:

Dog 14.—A brown and white mongrel terrier, weight 14.7 kg.

March 13, 1915. An abdominal operation was performed, with good recovery.

March 17, 1915. The dog appears rather listless for the first time. The urine contains a trace of albumin and a few isolated white blood corpuscles. Phenolsulphonephthalein excretion, 40 per cent. Urea nitrogen in the blood, 15 mg.

March 19, 1915. Phenolsulphonephthalein, 32 per cent. Total nonprotein nitrogen in the blood, 57 mg.; urea nitrogen, 33 mg.

March 20, 1915. Seventh day since operation. Total nonprotein nitrogen in the blood, 75 mg.; urea nitrogen, 53 mg. Phenolsulphonephthalein output, 11 per cent.

Four p. m. Operation: Double dorso-lumbar incision. The rubber bands were removed. The dog was catheterized at the time of operation.

March 21, 1915. Nine a. m. Seventeen-hour specimen of urine, 290 c.c., contained total nitrogen, 6.59 gm.; urea nitrogen, 5.10 gm. Total nonprotein nitrogen of blood, 42 mg.; urea nitrogen, 10 mg. The amount of urea excreted in the urine, 10.30 gm., corresponds closely to the theoretical amount, 11.10 gm., lost from the organism according to the calculation of Marshall and Davis.¹⁰ Phenolsulphonephthalein excretion, 40 per cent.

March 22, 1915. The general condition is excellent. Blood: Total nonprotein nitrogen, 33 mg.; urea nitrogen 7 mg. Phenolsulphonephthalein excretion, 68 per cent.; urine output, 365 c.c. on intake of 500 c.c. water.

April 10, 1915. The dog has continued to improve in general condition. Function normal since March 22. Today left nephrectomy was performed—lumbodorsal incision. The kidney is normal in size. On section the ureter and pelvis are slightly dilated. Histologic section showed normal glomeruli, moderate granular degeneration of tubular epithelium, slight dilatation of tubules and vascular congestion just beneath the pelvic mucosa, and in one spot 1 mm. in diameter, polymorphonuclear infiltration.

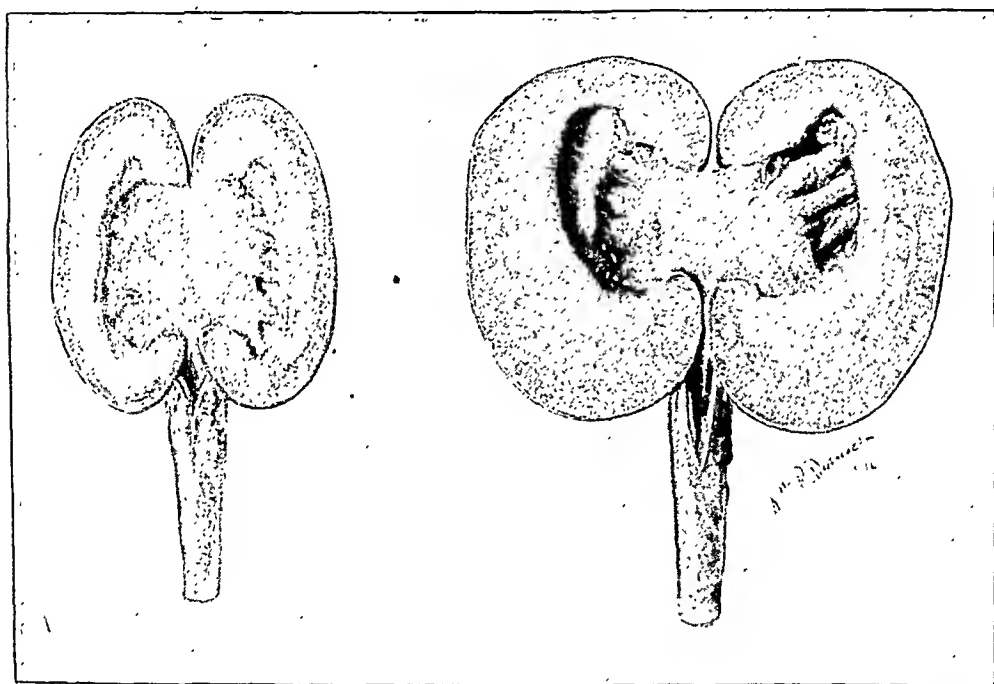


Fig. 5.—Kidneys of Dog 12. Severe damage to the kidney from prolonged partial ureteral obstruction.

April 17, 1915. Phenolsulphonephthalein excretion, 43 per cent. in one hour (intramuscularly). Blood urea nitrogen, 22 mg.

April 22, 1915. Water intake, 200 c.c. Urine output, 196 c.c. Specific gravity, 1.037. The dog has recovered his ability to concentrate urine.

June 11, 1915. Eighty-fourth day since removal of bands. The general condition has been excellent since April 22. Yesterday urea nitrogen in blood, 14 mg. Today phenolsulphonephthalein output, 71 per cent. The dog was sacrificed.

Necropsy.—The right kidney is normal in appearance except for a slight but obvious dilatation of the pelvis and also the ureter above the site of the band.

Histology.—There is no evidence of acute inflammatory infiltration. No increase in connective tissue. With the exception of slight tubular dilatation the parenchyma appears normal.

The foregoing experiment demonstrated conclusively that the kidneys after being subjected to an increased intra-ureteral pressure for a period of seven days were able to excrete urea and phenolsulphonephthalein in a normal manner within forty-eight hours after the removal of the obstruction (Fig. 6).

The left kidney, removed three weeks after operation, beside showing pelvic and tubular dilatation, had definite tubular cell changes along with a mild infection of the pelvic mucosa. This latter finding is of interest, in that the right kidney, removed sixty-three days later, was entirely free from inflammatory changes and was practically normal in every respect. The natural conclusion would be that during the seven days of back pressure a mild pyelitis was set up, but on removal of the

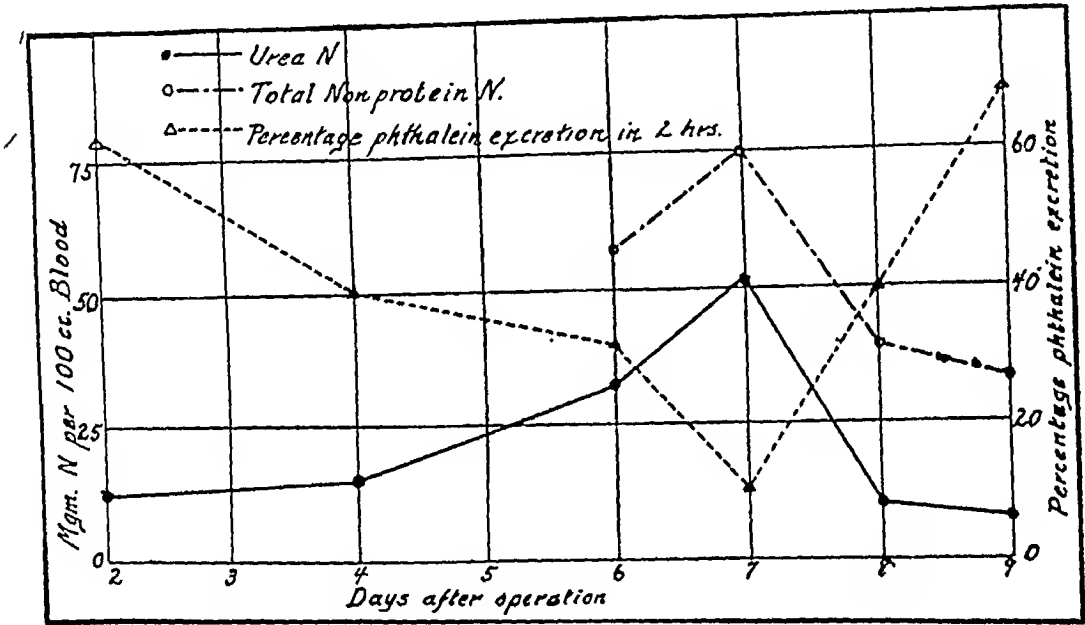


Fig. 6.—Dog 14. Curve showing recovery of function as indicated by blood and urine studies after the removal of the bands. The bands were removed on the seventh day.

obstruction, free drainage, and return of normal renal function resulted in a complete recovery before the end of the experiment, eighty-four days following operation.

In a second experiment (Dog 13) the bands were removed four days after their original insertion. The urea nitrogen of the blood was only slightly higher than normal, but the phenolsulphonephthalein excretion was markedly retarded. Following the removal of the obstruction both the urea content of the blood and phenolsulphonephthalein output were normal (within forty-eight hours, as in the case of Dog 14) and remained so until the dog was sacrificed seventy-seven days later (Table 7). The trace of albumin and the few pus cells found in the urine during the latter portion of this period were due to the presence of a low grade chronic pyelitis and cystitis.

Pathology.—Both kidneys appear normal. Ureters slightly larger above the site of the bands. On section the pelvic mucosa seems a little thickened and the pelvis itself is very slightly dilated.

Histology.—There are scattered isolated areas of round and plasma cell infiltration just beneath the pelvic mucosa. These are less numerous in the left kidney; kidney parenchyma normal.

Similar experiments were carried out on three additional animals, Nos. 11, 22, 23, the ureteral obstruction being removed on the third and fourth days. Normal function was present within three or four days in all of the animals. Dog 22 was of interest in that on the day previous to the removal of the obstruction, coincident with a fall of 30 to 25 mg. in the urea nitrogen content of the blood, there was an increase both in the volume of the urine, 135 to 200 c.c., and in the urea output, 2.92 to 4.56 gm., though the phenolsulphonephthalein excretion was only 16 per cent. It would seem that the increased urea content of the blood was exerting a diuretic effect on the diseased kidney. With the removal of the bands on the following day, both the phenolsulphonephthalein output and the urea content of the blood were normal within forty-eight hours.

Subsequent functional studies on these three animals were carried out over periods of from one to four months, and repeated tests demonstrated normal excretory ability. The findings at necropsy were similar to those of Dogs 14 and 13.

TABLE 7.—DATA FROM EXPERIMENT ON DOG 13

Dog 13. Weight 7.4 Kg. Intake: Water, 300 C.c.; sodium chlorid, 8 Gm. daily.

Date	Day of Operation	Blood Urea N, Mg.	Urine					
			Amount, C.c.	Reaction	Urea N, Gm.	Phthal-ein, 2 Hr.	Albu-min	Sedl-ment
12/15	..	10	52	Neg.	Neg.
1/ 7	295	Acid				
1/ 8	155	Acid				
1/10	1	Acid				
1/11	2	..	55	Acid				
1/12	3	30	150	Acid	0.34			
1/13	4	38	70	Acid	0.43	..	Plus	
1/14	5*	31	150	Acid	1.03	8	Plus	
1/15	6	16	230	Acid	52	Plus	
1/16	7	15	145	Acid	1.21	56	Neg.	
1/17	8	..	128	Acid	1.05	..	Neg.	
1/20	11	10	67	Plus	Pus cells
2/18	24	7	61	Neg.	Neg.
3/11	62	10	56	Plus	
3/29	80	7	65	Neg.	Pus cells (rare)

* Removal of bands.

In the previous five animals the ureteral obstruction was removed within two to seven days after the production of the increased back pressure. Functional studies at the time of the second operation indicated renal lesion of essentially the early acute type. In all of these animals there was practically complete restoration of the normal renal condition within a few weeks' time. The method of removing the ureteral obstruction having proved satisfactory in these experiments, further functional studies with sodium chlorid were attempted in view of the theoretical possibility that a mechanism is concerned in the excretion of this electrolyte different from that influencing the elimination of phenolsulphonaphthalein and urea. The results of this work are to be published in a subsequent paper.

DISCUSSION OF FUNCTIONAL RESULTS

The study of renal conditions in these experiments clearly indicates their division into two distinct types, the acute and the chronic. In Group 1 and in the early stage of the experiments in which the ureteral obstruction was removed, the functional results are typically those of acute renal insufficiency. On the other hand, in Group 2, functional changes were much slower in development and varied greatly from time to time. During the terminal period certain excretory products were well eliminated almost until death.

In the animals showing the acute type of renal impairment the excretion of phenolsulphonaphthalein was soon not more than 10 per cent., while at the same time the urea nitrogen of the blood rose rapidly to 61 to 100 mg. per 100 c.c. There was an initial decrease in the output of urine which usually continued to diminish until anuria was present, though in two animals this initial diminution in the amount of urine was followed by a short period of polyuria, with a corresponding increase in the nitrogenous excretion. This anomalous condition of an increased excretion of nitrogenous material accompanying a high nitrogen content in the blood was noted by Keith and Snowden in experimental unilateral hydronephrosis¹ and by Mosenthal¹⁷ in experimental uranium nephritis, and might be explained by the increased urea in the blood exerting a diuretic effect on the partially damaged kidney. It seems evident that the initial increase of urea in the blood is due to the inability of the kidney to excrete this substance at the normal threshold, and that after reaching a certain higher concentration in the blood and tissues urea may be eliminated freely for a short period.

16. Marshall, E. K., and Davis, D. M.: Urea: Its Distribution In and Elimination From the Body, *Jour. Biol. Chem.*, 1914, **18**, 53.

17. Mosenthal, H. O.: Nitrogen Metabolism and the Significance of the Non-protein Nitrogen of the Blood in Experimental Uranium Nephritis, *THE ARCHIVES INT. MED.*, 1914, **14**, 844.

The very high nonprotein nitrogen content of the blood found in this type is chiefly due to the great increase in urea.

In the chronic type of reaction, the functional picture before the terminal period was much more varied than in the acute group. The volume of urine was always increased and of a low specific gravity. The kidney appeared to be capable of separating the waste products of metabolism from the blood, but at a lower concentration. The output of phenolsulphonephthalein showed marked fluctuations, varying from 10 per cent. to 60 per cent. in two hours, though the average in a number of determinations was always moderately diminished. The total nitrogen of the blood was never markedly increased (61 mg. in one instance), but the urea nitrogen showed greater variations (from 10 to 47 mg.) and reached a relatively higher figure. From these data it is evident that the kidneys subjected to a long-standing back pressure may present marked variations in functional capacity and yet a definite pathologic condition may be present. At one period the kidney may have the normal ability to excrete phenolsulphonephthalein and also nitrogen so that the amount of the latter in the blood is quite normal. At another time the kidneys may excrete a given substance normally while a second substance is retarded in the elimination, as was well shown on the nineteenth day in Dog 12—a phenolsulphonephthalein excretion of 63 per cent. while the urea nitrogen in the blood was 41 mg. The reverse conditions were present in Dog 11 on the sixty-eighth day, the phenolsulphonephthalein output being 28 per cent. and the urea nitrogen of the blood 11 mg. There are also times when both the urea in the blood and phenolsulphonephthalein excretion are abnormal; for example, Dog 11, one hundred and fifth day, phenolsulphonephthalein 5 per cent., urea nitrogen 30 mg. These findings emphasize the fact that single determinations of renal function with the methods used in this study may give an erroneous idea as to the underlying chronic kidney lesion.

Direct blood pressure estimations on two animals with chronic lesions—one in the fifth month—were 125 to 155 mm. of mercury. The latter figure has been obtained in normal animals so that in this type of renal lesion hypertension was not definitely present.

During the short terminal period of renal insufficiency in this chronic group the functional results differed in many respects from the acute type characteristic of Group 1. Renal excretion as a whole was markedly affected, but in spite of a low output of phenolsulphonephthalein and an accumulation of nitrogen in the blood, there was a definite polyuria lasting for several days. Gradually the nitrogen in the blood increased, though there was a moderate and remarkably constant daily excretion in the urine. This result would indicate that

the capacity of the kidney to eliminate nitrogenous substances from the blood was limited, and that when their production in the body increased above this amount the blood and tissue content must necessarily rise. Contrary to what was found in Group 1, there was little evidence that the increased urea in the blood was exerting a diuretic action on the diseased kidney. The finding of a definite increase in the creatin and creatinin content of the blood and a high blood hydrogen-ion concentration indicates a similarity of the functional changes in this experimental condition with those often found in clinical cases of terminal chronic nephritis.

In five experiments, with removal of the ureteral obstruction, normal renal function was rapidly restored. The ability of the kidney to recover after being subjected to increased intra-ureteral pressure depends on the degree and duration of back pressure. The rôles played by these two factors are well indicated by two experiments. Dog 14 recovered complete renal function after an increased intra-ureteral pressure of seven days, while in the case of Dog 5, Group 1, removal of the obstruction on the fifth day did not prevent death three days later. Thus, it seems clear that in order to obtain complete recovery of function in this acute type of lesion, the obstruction must be relieved within a few days after the initial lesion has been produced, otherwise acute insufficiency rapidly ensues or a chronic lesion later develops.

In order to determine this question of functional recovery, Kawasoye¹⁸ tied off one ureter in each of seven rabbits and then relieved the obstruction after varying periods of time. He found complete restoration of functional ability, as shown by the excretion of indigocarmine, took place after four days, incomplete restoration after seven to fourteen days and after twenty-one days no dye at all was secreted. Barney¹⁹ reports a clinical case in which both ureters were ligated accidentally at operation. The left ureter was freed in forty-eight hours and the right on the sixth day. The patient made a good recovery and the urine was negative for albumin and casts. These results are in harmony with the findings in the present experiments. They also suggested the removal of the partial obstruction at a later period of the kidney lesion. This experiment was carried out on Dog 9 on the one hundred and forty-third day after the placing of the obstruction. No marked change in the renal condition resulted within the next week with the exception of a rather low output of urine for two days subsequent to the removal of the bands. The phenolsul-

18. Kawasoye, M.: Experimentelle Studien zum künstlichen Ureterverschluss. *Ztschr. f. Gynäk. Urol.*, 1911-1912, **3**, 172.

19. Barney, J. D.: The Effects of Ureteral Ligation, *Experimental and Clinical, Surg., Gynec. and Obst.*, 1912, **15**, 290.

phonephthalein excretion and nitrogen values in the blood and urine were influenced little or not at all by the operation. Anatomically, there was no apparent decrease in the ureteral or pelvic dilatation (Fig. 2). This single experiment at least indicates that after long continued back pressure associated with pelvic infection, removal of the obstruction produces little immediate functional improvement.

DISCUSSION OF PATHOLOGIC RESULTS

The pathologic picture resulting from partial obstruction of the ureter was demonstrated by Scott²⁰ to be similar to that of hydronephrosis following complete ureteral ligation. The chief factors determining the character of the lesions were the degree and duration of the back pressure. Both Scott²⁰ and Kawasoye¹⁸ pointed out the slower development of these renal changes when the ureter was only partially occluded. Their findings were confirmed at necropsy in the sixteen animals subjected to functional studies in these experiments. The extent of the back pressure was not determined by manometer readings in this study because early in the work accurate pressure estimations were found to be unsatisfactory. The pressure was roughly gaged by the degree of ureteral dilatation and appearance of the ureteral wall above the site of the obstruction. With large thin-walled ureters chronic renal lesions were always present, while the acute processes were accompanied by a ureter dilated but comparatively thick walled.

The changes found in the kidney may be classed as acute and chronic. The acute process, occurring during the first week, was characterized in the gross by a kidney normal or increased in size, engorged capsular veins, a dilated pelvis and ureter. Renal congestion was also, as a rule, present. On histologic examination the tubules were dilated, the extent of dilatation varying within wide limits, and the lumina often contained granular material. The epithelial cells were usually granular in appearance, with well preserved nuclei, though occasionally the cells were flattened and cuboidal in shape. The glomeruli appeared quite normal. Connective tissue infiltration was present in only one instance during the first week. The tissues beneath the pelvic mucosa were, as a rule, congested and in two animals sacrificed within two or three days of the initial obstruction, definite polymorphonuclear infiltration was present. Kawasoye¹⁸ reports the presence of leukocytes in the pelvic urine two days after ureteral ligation.

The anatomic findings in the kidneys of animals in which the rubber bands had been removed during the acute lesion were of inter-

20. Scott, G. D.: *Experimental Hydronephrosis*, Surg., Gynec. and Obst., 1912, 15, 296.

est. These were examined from five weeks to several months after the removal of the obstruction. The renal parenchyma in all was practically normal, though in the pelvis in three instances there was evidence of an old inflammatory process. This pelvic lesion, with the back pressure removed, apparently had little effect on the parenchyma cells, as these were normal in appearance and capable of carrying on normal function.

Kidneys subjected to a prolonged high intra-ureteral pressure showed interesting chronic changes. In the gross the two kidneys were always unequal in size, one much larger than normal, while the opposite organ was often small and atrophied. The capsular veins were always prominent, the ureter and pelvis dilated, the latter frequently forming a cyst-like cavity with a cortex reduced to a thin band of connective tissue. Microscopically, the connective tissue infiltration was the most striking pathologic process even at the end of three weeks. The glomeruli were as a rule shrunk and Bowman's capsule invariably thickened. The tubular epithelium usually showed granular degeneration, sometimes the nuclei were pyknotic and the cell boundaries could not be differentiated. The lumina frequently contained granular debris and casts. In other kidneys the tubular epithelium was compressed and quite flat in appearance. Some kidneys were remarkably free from any acute inflammation, while in others the medulla showed a zone of infiltration bordering on a pelvic cavity containing a mass of necrotic inflammatory material.

The rôle played by infection in the kidneys subjected to increased ureteral pressure is often difficult of interpretation. In the acute stage early acute inflammatory processes were observed in the pelvic mucosa within forty-eight hours of the initial obstruction, and in one experiment (Dog 25) in seventy-two hours the whole renal parenchyma was infiltrated with polymorphonuclear leukocytes.

The fact that early removal of the obstruction allowed quick restoration of the parenchyma cells in spite of the continued presence of pelvic infection, indicates that the pressure factor is of primary importance in the acute process. In the experiments in which hydronephrotic sacs finally developed, the part played by infection is somewhat harder of interpretation. With a mild pelvic infection from the onset, as previously described in the acute stage, there is the possibility of its further invading the kidney tissue with the subsequent formation of connective tissue. The histologic studies of Scott,²⁰ Amos²¹ and Bradford²² in experimental hydronephrosis would indicate that

21. Amos, B. S.: On the Effect of Ligation of One Ureter, *Jour. Path. and Bact.*, 1915, **10**, 265.

22. Bradford, J. Rose: Observations Made on Dogs to Determine Whether Obstruction of the Ureter Would Cause Atrophy of the Kidney, *Brit. Med. Jour.*, 1897, **2**, 1720.

phonephthalein excretion and nitrogen values in the blood and urine were influenced little or not at all by the operation. Anatomically, there was no apparent decrease in the ureteral or pelvic dilatation (Fig. 2). This single experiment at least indicates that after long continued back pressure associated with pelvic infection, removal of the obstruction produces little immediate functional improvement.

DISCUSSION OF PATHOLOGIC RESULTS

The pathologic picture resulting from partial obstruction of the ureter was demonstrated by Scott²⁰ to be similar to that of hydronephrosis following complete ureteral ligation. The chief factors determining the character of the lesions were the degree and duration of the back pressure. Both Scott²⁰ and Kawasoye¹⁸ pointed out the slower development of these renal changes when the ureter was only partially occluded. Their findings were confirmed at necropsy in the sixteen animals subjected to functional studies in these experiments. The extent of the back pressure was not determined by manometer readings in this study because early in the work accurate pressure estimations were found to be unsatisfactory. The pressure was roughly gaged by the degree of ureteral dilatation and appearance of the ureteral wall above the site of the obstruction. With large thin-walled ureters chronic renal lesions were always present, while the acute processes were accompanied by a ureter dilated but comparatively thick walled.

The changes found in the kidney may be classed as acute and chronic. The acute process, occurring during the first week, was characterized in the gross by a kidney normal or increased in size, engorged capsular veins, a dilated pelvis and ureter. Renal congestion was also, as a rule, present. On histologic examination the tubules were dilated, the extent of dilatation varying within wide limits, and the lumina often contained granular material. The epithelial cells were usually granular in appearance, with well preserved nuclei, though occasionally the cells were flattened and cuboidal in shape. The glomeruli appeared quite normal. Connective tissue infiltration was present in only one instance during the first week. The tissues beneath the pelvic mucosa were, as a rule, congested and in two animals sacrificed within two or three days of the initial obstruction, definite polymorphonuclear infiltration was present. Kawasoye¹⁸ reports the presence of leukocytes in the pelvic urine two days after ureteral ligation.

The anatomic findings in the kidneys of animals in which the rubber bands had been removed during the acute lesion were of inter-

20. Scott, G. D.: *Experimental Hydronephrosis*, Surg., Gynec. and Obst., 1912, 15, 296.

est. These were examined from five weeks to several months after the removal of the obstruction. The renal parenchyma in all was practically normal, though in the pelvis in three instances there was evidence of an old inflammatory process. This pelvic lesion, with the back pressure removed, apparently had little effect on the parenchyma cells, as these were normal in appearance and capable of carrying on normal function.

Kidneys subjected to a prolonged high intra-ureteral pressure showed interesting chronic changes. In the gross the two kidneys were always unequal in size, one much larger than normal, while the opposite organ was often small and atrophied. The capsular veins were always prominent, the ureter and pelvis dilated, the latter frequently forming a cyst-like cavity with a cortex reduced to a thin band of connective tissue. Microscopically, the connective tissue infiltration was the most striking pathologic process even at the end of three weeks. The glomeruli were as a rule shrunken and Bowman's capsule invariably thickened. The tubular epithelium usually showed granular degeneration, sometimes the nuclei were pyknotic and the cell boundaries could not be differentiated. The lumina frequently contained granular debris and casts. In other kidneys the tubular epithelium was compressed and quite flat in appearance. Some kidneys were remarkably free from any acute inflammation, while in others the medulla showed a zone of infiltration bordering on a pelvic cavity containing a mass of necrotic inflammatory material.

The rôle played by infection in the kidneys subjected to increased ureteral pressure is often difficult of interpretation. In the acute stage early acute inflammatory processes were observed in the pelvic mucosa within forty-eight hours of the initial obstruction, and in one experiment (Dog 25) in seventy-two hours the whole renal parenchyma was infiltrated with polymorphonuclear leukocytes.

The fact that early removal of the obstruction allowed quick restoration of the parenchyma cells in spite of the continued presence of pelvic infection, indicates that the pressure factor is of primary importance in the acute process. In the experiments in which hydronephrotic sacs finally developed, the part played by infection is somewhat harder of interpretation. With a mild pelvic infection from the onset, as previously described in the acute stage, there is the possibility of its further invading the kidney tissue with the subsequent formation of connective tissue. The histologic studies of Scott,²⁰ Amos²¹ and Bradford²² in experimental hydronephrosis would indicate that

21. Amos, B. S.: On the Effect of Ligation of One Ureter, *Jour. Path. and Bact.*, 1915, **10**, 265.

22. Bradford, J. Rose: Observations Made on Dogs to Determine Whether Obstruction of the Ureter Would Cause Atrophy of the Kidney, *Brit. Med. Jour.*, 1897, **2**, 1720.

the connective tissue sac could be formed without any, or with little, associated infectious process. Then again, bacteriologic examination has revealed hydronephrotic sacs containing sterile fluid.¹⁹ Thus the results of previous investigators and the present experiments offer conclusive evidence that the increased back pressure is mainly responsible for the marked renal connective tissue infiltration, and that the secondary infectious process plays a minor though definite rôle.

SUMMARY

Bilateral, partial ureteral obstruction in dogs produced changes in renal function and structure.

The severity of the renal lesion primarily depended on the amount of pressure exerted by the elastic band on the ureteral wall. With a high pressure functional and pathologic results were similar to those following high ureteral ligation, though the obstruction was incomplete. Slight or moderate pressure slowly produced a chronic lesion.

In the acute lesion due to high intra-ureteral pressure, the kidneys ceased to carry on their function within a few days and the death of the animal quickly followed.

Evidence of impaired renal function resulting from a moderately increased intra-ureteral pressure was not always found during the early stages, but as the lesion progressed, decreased function was invariably present. Diminished function, as shown by the phenolsulphonephthalein excretion and urea content of the blood, was not incompatible with the general good health of the animal for a period as long as five months. During the subsequent acute terminal stage, there was marked renal insufficiency as indicated by a low phenolsulphonephthalein excretion, increased urea and creatinin content and increased hydrogen-ion concentration of the blood.

Rapid restoration of normal renal function took place when the ureteral obstruction was removed within a week. Removal of the obstruction in one experiment after a chronic lesion had developed, produced little immediate functional improvement.

The progress and extent of the pathologic lesion in the kidney depended on the amount and duration of the intra-ureteral pressure, and, in a lesser degree, on the invariable secondary pelvic infection. These factors resulted in anatomic changes ranging from slight dilatation of ureter and pelvis to hydronephrotic sac formation. Histologic examination as early as the second day after the initial obstruction revealed congestion and granular degenerative processes. Beginning with the seventh day, these changes were accompanied by connective tissue infiltration which gradually increased until eventually the kidney parenchyma was replaced by a connective tissue sac.

The authors wish to express their appreciation and thanks to Dr. D. M. Davis for the histologic notes in this study.

THE NONPROTEIN CONSTITUENTS OF EDEMA FLUIDS *

W. DENIS, PH.D.

WITH THE ASSISTANCE OF

A. S. MINOT, A.B.

BOSTON

Although many investigations have been published regarding the proteins of edema fluids, the available data regarding their nonprotein constituents are exceedingly meager. In the standard and frequently copied analyses to be found in most textbooks these bodies are almost universally grouped together under the vague title of "extractives," and are to be found recorded under this general heading, together with the more elaborate analyses of the protein and inorganic constituents. By means of the micromethods which have come into general use during the past five years we now know, in a general way at least, the level at which the more common nonnitrogenous bodies are maintained in the blood in health and in disease. Investigations by modern methods along this line have, however, been extended in only a few instances¹ to body fluids other than blood.

In view of this lack of available data it has seemed worth while to publish the results obtained by the analysis of a small number of edema fluids in which we have made determinations of most of the ordinary nonprotein bodies occurring in such material.

In Table 1 are presented the results obtained on a series of fluids (pleuritic, ascitic and hydrocele) which were selected from the available material because they illustrate the chemical variations ordinarily to be met with in unselected clinical material.

The methods of analysis used were as follows:

Total Solids.—Ten c.c. of the fluid was dried to constant weight in a platinum dish placed in an air bath kept at a temperature of 100 c.c.

Total Protein.—By calculations from the total nitrogen, which was determined by the Kjeldahl-Gunning method.

Nonprotein Nitrogen and Urea.—By the direct nesslerization methods of Folin and Denis.²

Uric Acid.—By the method of Folin and Denis as modified by Myers and Fine.³

* Submitted for publication July 3, 1917.

* From the Chemical Laboratory of the Massachusetts General Hospital.

1. Fine, M. S., and Myers, V. C.: *Proc. Soc. for Exper. Biol. and Med.*, 1916, **13**, 126. Kahn and Neal: *ibid.*, 1916, **14**, 26.

2. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1916, **26**, 473.

3. Myers, V. C., and Fine, M. S.: *The Significance of the Uric Acid, Urea and Creatinin of the Blood in Nephritis*, *THE ARCHIVES INT. MED.*, 1916, **17**, 570.

TABLE 1.—RESULTS OF ANALYSIS OF EDEMA—

No.	Description	Specific Gravity	Mg. per 100 C.c. Fluid	
			Total Protein	Nonprotein Nitrogen
2	Chest fluid; cardiac.....	1.016	1,950	25
12	Pleuritic fluid; pleurisy.....	1.032	3,981	36
3	Ascitic fluid; tuberculous peritonitis.....	1.040	3,375	38
9	Ascitic fluid; cirrhosis of liver.....	1.012	712	33
6	Ascitic fluid; cirrhosis of liver.....	1.008	916	28
17	Ascitic fluid; cirrhosis of liver.....	1.015	1,906	37
18	Same patient as No. 17, 5 days later.....	1.013	1,412	41
27	Ascitic fluid; portal obstruction.....	1.017	1,956	25
28	Same patient as No. 27, 6 days later.....	1.015	1,750	17
31H	Hydrocele fluid	1.029
32H	Same patient as 31 H, 24 hours later.....	1.030	4,250	..
42H	Hydrocele fluid	1.022	3,637	43
47H	Hydrocele fluid	1.019	3,681	39
24H	Hydrocele fluid	1.025	6,431	30
14H	Hydrocele fluid	237	3

TABLE 2.—RESULTS OF ANALYSIS OF ASCITIC FLUID—

Date	Volume, C.c.	Sp. Gr.	Mg. per 100 C.c. Fluid				
			Total Protein	Nonprotein Nitrogen	Urea Nitrogen	Uric Acid	Creatinin
11/15	8,000	1.014	1,781	26	14	...	0.5
11/17	5,000	1.016	2,156	38	19	...	0.7
11/27	10,000	1.012	1,269	27	10	1.8	...
12/ 5	5,000	1.012	1,231	29	10	4.6	0.5
12/11	3,500	1.012	1,250	29	13	3.2	0.6
12/18	3,700	1.011	1,125	29	8	1.6	0.9
12/26	3,280	1.011	1,119	11	7	1.5	...
1/ 2	3,620	1.011	962	29	10	1.8	...
1/10	3,280	1.011	1,119	17	9	1.8	...
1/19	3,300	1.011	1,400	23	10
2/ 1	2,500	1.012	1,400	26	12	2.1	...
2/ 6	1,970	1.013	1,594	27	12

—FLUIDS FOR NONPROTEIN BODIES

Mg. per 100 C.c. Fluid							
Urea Nitrogen	Uric Acid	Creatin + Creatinin	Creatin	Total Fat	Total Cholesterol	Sugar	Sodium Chlorid
11	...	3.0	1.0	256	43	95	650
..	...	6.6	1.2	330	115	110	
13	...	6.0	...	372	77	86	
..	1.2	2.0	0.6	160	...	112	640
11	2.0	190	40	145	500
18	176	38	140	
21	174	...	145	
11	1.9	3.4	0.62	256	72	100	720
9	1.8	2.4	0.42	408	55	134	800
..	444	59	90	
..	5.6	6.6	...	416	57	95	600
22	1.1	9.6	1.6	148	40	99	680
..	3.0	4.5	1.1	236	28	117	700
..	...	8.9	1.9	362	81	...	640
14							

—FROM A PATIENT WITH CIRRHOSIS OF THE LIVER

Mg. per 100 C.c. Fluid					Remarks
Creatin	Total Fat	Total Cholesterol	Sugar	Sodium Chlorid	
2.19	256	31	Ward diet
2.62	184	15	130	...	Ward diet
...	124	13	120	660	Ward diet
1.60	146	13	130	680	
1.25	146	12	...	700	High protein diet with much meat started November 30; average urinary nitrogen per day 9.0 gm.; average uric acid excretion 0.43 gm.; blood nonprotein nitrogen 37 mg.
1.20	120	24	130	700	High protein diet with meat continued; average urinary nitrogen per day 9.4 gm.; average uric acid excretion 0.44 gm.; blood nonprotein nitrogen 38 mg.; urea 19 mg.; uric acid 3.5 mg.; cholesterol 205 mg.
....	112	30	130	740	Low protein diet started December 11; average urinary nitrogen 4 gm.; average uric acid excretion 0.27 gm.
....	115	24	130	740	Low protein diet continued; average urinary nitrogen 3.6 gm.; average uric acid excretion 0.25 gm.; blood nonprotein nitrogen 18.0 mg.; uric acid 1.8 mg.; cholesterol 195 mg.
....	117	29	130	720	Returned to former high protein diet with meat
....	112	44	120	740	December 25; nonprotein nitrogen of blood 38 mg.
....	168	20	130	760	Ward diet
....	176	29	130	760	January 13 started high cholesterol diet; 14 egg yolks and 6 gm. cholesterol per day
					Ward diet

Creatin and Creatinin.—By Folin's methods.⁴

Total Fat and Cholesterol.—By Bloor's⁵ micromethods.

Sugar.—By the method of Lewis and Benedict,⁶ as modified by Myers and Bailey.⁷

Sodium Chlorid.—By the Volhard method, after precipitating the proteins by means of magnesium sulphate and acetic acid.

It was not possible to obtain blood from the patients the results of whose fluids are given in Table 1. Below are presented the data obtained on a few cases of ascites, pleurisy and hydrothorax in which bloods taken at the time of paracentesis were examined by the same method used in the analysis of the fluid.

Ascitic Fluid 1.—Man, aged 60 years. Peritonitis (tubercular). Volume of fluid obtained, 3,800 c.c.; a clear, straw colored liquid, specific gravity 1.020.

Determination	—Mg. Per 100 C.c.—	
	Fluid	Blood
Total solids.....	6,740.0
Total protein.....	4,919.0
Nonprotein nitrogen.....	31.0	30.0
Urea nitrogen.....	15.0	12.0
Uric acid.....	2.8
Creatinin	0.7
Creatin + creatinin.....	4.8	7.7
Sugar	141.0	140.0
Total fatty acids.....	408.0	560.0
Total cholesterol.....	89.0	208.0
Sodium chlorid.....	720.0

Ascitic Fluid 2.—Man, aged 56 years. Cirrhosis of the liver; alcoholism. Last tap eleven days previously; volume of fluid obtained, 6,300 c.c. Specific gravity 1.012.

Determination	—Mg. Per 100 C.c.—	
	Fluid	Blood
Total solids.....	2,315.0
Total protein.....	1,693.0
Nonprotein nitrogen.....	56.0	52.0
Urea nitrogen.....	28.0	26.0
Uric acid.....	3.8	3.6
Creatinin	1.0	1.3
Creatin + creatinin.....	3.3	9.2
Sugar	155.0	90.0
Total fatty acids.....	79.0	866.0
Total cholesterol.....	25.0	276.0
Sodium chlorid.....	800.0

4. Folin, O.: Jour. Biol. Chem., 1914, **17**, 475.

5. Bloor, W. R.: Jour. Biol. Chem., 1914, **17**, 377; 1916, **24**, 227.

6. Lewis, R. C., and Benedict, S. R.: Jour. Biol. Chem., 1915, **20**, 61.

7. Myers, V. C., and Bailey, C. V.: Jour. Biol. Chem., 1916, **24**, 147.

Ascitic Fluid 3.—Woman, aged 45 years. Cirrhosis of the liver; syphilis; last tap nine days previously; volume of fluid obtained, 5,400 c.c.; specific gravity 1.012.

Determination	—Mg. Per 100 C.c.—	
	Fluid	Blood
Total solids.....	2,234.0
Total protein.....	1,400.0
Nonprotein nitrogen.....	25.0	26.0
Urea nitrogen.....	12.0	12.0
Uric acid.....	2.0	2.0
Creatinin	0.8	1.3
Creatin + creatinin.....	3.1	7.3
Sugar	100.0	93.0
Total fatty acids.....	90.0
Total cholesterol.....	22.0
Sodium chlorid.....	600.0

Ascitic Fluid 4.—Woman, aged 66 years. Diagnosis, probably portal obstruction; last tap eleven days previously; volume of fluid obtained, 5,500 c.c.; specific gravity 1.011.

Determination	—Mg. Per 100 C.c.—	
	Fluid	Blood
Total solids.....	1,820.0
Total protein.....	875.0
Nonprotein nitrogen.....	22.0	22.0
Urea nitrogen.....	11.0	11.0
Uric acid.....	1.8
Creatinin	0.5	1.1
Creatin + creatinin.....	2.6	8.3
Sugar	113.0	90.0
Total fatty acids.....	62.0	666.0
Total cholesterol.....	20.0	166.0
Sodium chlorid.....	700.0

Chest Fluid 1.—Man, aged 19 years. Acute pleurisy; first tap; volume of fluid obtained, 1,260 c.c. A clear straw colored fluid of specific gravity 1.026, which clotted rapidly.

Determination	—Mg. Per 100 C.c.—	
	Fluid	Blood
Total solids.....	6,585.0
Total protein.....	5,543.0
Nonprotein nitrogen.....	36.0	28.0
Urea nitrogen.....	16.0	14.0
Uric acid.....	3.3	3.0
Creatinin	0.5
Creatin and creatinin.....	5.3	7.8
Sugar	101.0	103.0
Total fatty acids.....	328.0	810.0
Total cholesterol.....	84.0	140.0

Chest Fluid 2.—Man, aged 25 years. Tuberculosis; pleurisy; volume of fluid obtained, 1,500 c.c. A deep yellow liquid, specific gravity 1.022, from which fibrin began to separate soon after removal from the body; total cells, 800 per c.mm.

Determination	—Mg. Per 100 C.c.—	
	Fluid	Blood
Total solids.....	5,952.0
Total protein.....	4,548.0
Nonprotein nitrogen.....	22.0	25.0
Urea nitrogen.....	11.0	12.0
Uric acid.....	2.5	2.0
Creatinin	0.8
Creatin and creatinin.....	6.8	8.9
Sugar	95.0	90.0
Total fatty acids.....	650.0	910.0
Total cholesterol.....	108.0	250.0
Sodium chlorid.....	680.0

Chest Fluid 3.—Man, aged 39 years. Diagnosis, "probably malignant growth;" third tap in ten days; a dark brown fluid, red cells, 1,000,000 per c.mm.; specific gravity 1.016.

Determination	—Mg. Per 100 C.c.—	
	Fluid	Blood
Total solids.....	5,225.0
Total protein.....	3,587.0
Nonprotein nitrogen.....	27.0	28.0
Urea nitrogen.....	13.5	14.0
Uric acid.....	3.0	2.8
Creatinin	0.8	1.0
Creatin and creatinin.....	3.5	7.4
Sugar	110.0	111.0
Total fatty acids.....	240.0	1,000.0
Total cholesterol.....	86.0	333.0
Sodium chlorid.....	680.0

Chest Fluid 4.—Man, aged 42 years. Cardiac, general edema; volume of fluid obtained, 1,350 c.c.; a slightly cloudy, pale yellow fluid, of specific gravity 1.018.

Determination	—Mg. Per 100 C.c.—	
	Fluid	Blood
Total solids.....	4,400.0
Total protein.....	3,324.0
Nonprotein nitrogen.....	23.0	26.0
Urea nitrogen.....	11.0	13.0
Uric acid.....	2.4	2.6
Creatinin	1.1
Creatin and creatinin.....	4.6	8.0
Sugar	117.0
Total fatty acids.....	226.0
Total cholesterol.....	89.0
Sodium chlorid.....	700.0

Chest Fluid 5.—Woman, aged 47 years. Mitral stenosis and regurgitation; anasarca; first tap; volume of fluid obtained, 1,400 c.c.; a pale yellow, clear fluid, of specific gravity 1.010.

Determination	—Mg. Per 100 C.c.—	
	Fluid	Blood
Total solids.....	1,832.0
Total protein.....	763.0
Nonprotein nitrogen.....	32.0	34.0
Urea nitrogen.....	16.0	17.0
Uric acid.....	2.0
Creatinin	0.6
Creatin and creatinin.....	2.6
Sugar	109.0
Total fatty acids.....	90.0	824.0
Total cholesterol.....	39.0	240.0
Sodium chlorid.....	600.0

The results here presented indicate that the concentration of most of the nonprotein nitrogenous constituents belonging to the class of crystalloids, namely, urea, uric acid and creatinin, occur in edema fluids in about the same concentration as in the blood, a fact already pointed out for urea by Javal and Adler.⁸ While the sugar content of the pleuritic fluids is about that of normal blood, it is to be noted that in the case of the ascitic fluids, particularly those obtained from patients suffering from cirrhosis of the liver, it is notably high.

The figures obtained for total creatinin (creatin + preformed creatinin) are, on the other hand, lower than those obtained on whole blood. Wilson and Plass⁹ have recently published a criticism of the Folin method for the determination of creatin in blood, the method by means of which these determinations were made, in which it is said that this procedure may, on hemolyzed blood, give figures 100 per cent. greater than those obtained by the acetic acid method used by these authors, a method which in their opinion is theoretically less open to disturbing factors than is the method of picric acid precipitation. In plasma and in unhemolyzed blood they obtained fairly concordant results in parallel determinations made by the two methods. The same investigators have also pointed out the interesting fact that creatin occurs largely in the corpuscles; little, and, in some cases, none at all, have been found by them in human plasma.

The results presented here were obtained before the publication of the paper of Wilson and Plass, and it has therefore not been possible to make parallel determinations by their method on these fluids; as, however, the creatin and creatinin determinations reported were made

8. Javal and Adler: *Compt. rend Soc. de biol.*, 1906, **61**, 235. Wells and Hedenburg: *Jour. Infect. Dis.*, 1912, **2**, 349.

9. Wilson and Plass: *Jour. Biol. Chem.*, 1917, **29**, 413.

on unhemolyzed blood, and as the edema fluids examined contained, with one exception, no red cells, it is safe to conclude that the disturbing factors pointed out by Wilson and Plass were probably not operative in connection with the results presented here.

Considering the small number of cells occurring in edema fluids, the figures for creatin found in the case of these exudates and transudates is, in view of the findings of Wilson and Plass, surprising. It should be noted that while the creatin content of the fluids obtained from chronic cases is exceedingly low (compared to the level at which this product occurs in the blood), those obtained from the more acute cases present, as a rule, much higher values (Chest Fluid 2), a fact which may perhaps, in part, be accounted for by the higher cell content of fluids of the more acute type; although in considering this theory the possible influence of autolytic action should not be ignored.

The results obtained on the lipid constituents determined (total fat and cholesterol) are somewhat similar to those obtained with creatin. In fluids of the purely transudate type, the amounts of fat and cholesterol are small (Ascitic Fluids 3 and 4, Chest Fluid 5), while in exudates (Ascitic Fluid 7, Chest Fluid 1) the quantities of fat and of cholesterol present are much increased. Here again the relative number of cells present in the two types of fluids may be suggested as the cause of the difference in composition, for, as is well known, white cells are relatively rich both in neutral fat and in cholesterol.

The relatively small proportion of cholesterol to total fatty acids, if we take as a standard the analyses of "fasting" human blood published by Bloor,¹⁰ is also striking.¹¹

It is now recognized that the concentration of many of the non-protein constituents of the blood of normal persons may be influenced by diet; in cases of nephritis the effect is even more marked. Experimental data regarding the effect of diet on the nonprotein constituents of body fluids other than blood are, however, lacking. We have recently had the opportunity of making a series of observations on ascitic fluids obtained from a case of liver cirrhosis in which the patient was tapped at intervals of six or eight days, and have thus been able to observe the influence of changes in food intake on the composition of the transudate.

The subject of these experiments was an Italian, aged 51 years, weighing 138 pounds. The diagnosis was cirrhosis of the liver (alcoholic), ascites, hypertrophy and dilatation of the heart, mitral regurgi-

10. Bloor, W. R.: *Jour. Biol. Chem.*, 1916, 25, 477.

11. In considering the figures for total fatty acids the fact must be taken into account that the samples of blood were taken at the time of parasynthesis, which, in every case, was in the afternoon two to four hours after the mid-day meal.

tation and general arteriosclerosis. Omentopexy had been performed six years previously. The operation afforded some relief for about a year, but for the previous five years the patient had had to be tapped at gradually decreasing intervals. The results obtained on this patient are given in Table 2.

The experimental diets used have been one containing the maximum amount of protein the patient could be induced to take, one containing the smallest amount of protein on which we could keep him reasonably contented, and one in which an attempt was made definitely to increase the cholesterol intake. For purposes of comparison the results obtained on a number of samples of fluid which were collected while the patient was on ordinary house diet have been included.

As will be seen from Table 2 the response to changes in food intake was prompt. During the two periods of high protein and high purin feeding the uric acid, nonprotein nitrogen and urea of the blood showed values much greater than those observed during the succeeding days of low protein intake. The period of high cholesterol intake was also marked by a considerable increase in the amount of this body present in the fluid collected during this time. Practically no changes were observed in the content of the total protein of the fluid as a result of changes in protein intake, a finding in accord with the observations of Müller,¹² who found, in a patient with ascites due to a portal thrombosis, that an extremely high protein intake must be brought about before an increase in the amount of total protein in the ascitic fluid could be conclusively demonstrated.

SUMMARY

Results obtained by the quantitative examination of various types of edema fluids for their nonprotein constituents are presented. As a result of these analyses the following conclusions have been made:

1. That many of the nonprotein constituents of the fluids which belong to the class of crystalloids, among which may be mentioned urea, uric acid, and creatinin, occur in the same concentration in exudates and transudates as in the blood. The sugar content of ascitic fluids is somewhat higher than that of the blood, a finding not made in the case of the examples of pleuritic fluid analyzed.

In transudates, total creatin occurs only in small amounts. In fluids of the more purely exudate type it is present in considerably higher concentrations, frequently approaching closely the concentration found in whole blood.

12. Müller: *Deutsch. Arch. f. klin. Med.*, 1903, **76**, 563.

2. Fat and cholesterol occur in transudates in relatively small amounts. In fluids obtained from acute cases the content of fat and cholesterol rises and the former may at times approximate the concentrations found in blood.

3. In a patient with ascites from whom fluid was withdrawn every six to eight days, it was shown that the concentration of urea, uric acid and cholesterol in the fluid could be easily influenced by changes in diet.

A CASE OF CANTHARIDES POISONING WITH SPECIAL REFERENCE TO THE BLOOD-PICTURE*

SAMUEL T. LIPSITZ, M.D., AND A. J. CROSS, M.D.
ST. LOUIS

Poisoning by cantharides is not a common event in this country. When it does occur the tincture of cantharides is the preparation usually employed. Its action is well known. Briefly, when applied externally it acts as a rubefacient and after some hours it forms small blisters which later coalesce, producing large bullae. It is essentially a counterirritant. When taken internally, the lethal dose may be as low as 30 gm. or even less. Toxic doses produce severe irritation along the alimentary tract and in the genito-urinary system, with symptoms of collapse. It is said to circulate in the blood as an albuminate and is slowly excreted by the kidneys. Excepting the irritating effect on the mucous surfaces over which it passes in the process of elimination and its action on the genito-urinary system, it causes no marked changes in any of the internal organs. Cantharides produces a true acute nephritis with albuminuria, casts, passage of blood, suppression of urine and pain in the back. Characteristic and early symptoms are evidence of gastro-intestinal irritation; pain and soreness beneath the sternum and in the epigastrium; vomiting of blood; signs of acute nephritis with hematuria; violent pain in the lower dorsal region and in the small of the back; vesical tenesmus; frequent, scanty micturition; and priapism. The patient also shows more or less definite signs of shock. Death usually results from the arrest of renal function.

It is interesting to note that diuresis and polyuria are often early manifestations, but are soon followed by suppression and even anuria.

There do not appear to be any references in the literature to the condition of the blood in cantharides poisoning. The following report of a case is deemed of considerable interest because a clinical study of the blood was made and certain deviations from the normal were found. In the presence of severe and persistent nephritis and hematuria it would be reasonable to expect a definite secondary anemia. In this case it was surprising to find the contrary true, the patient presenting a most marked erythremia shortly after the incidence of the poisoning, and this continued, though to a somewhat less degree, for a number of days.

* Submitted for publication Aug. 4, 1917.

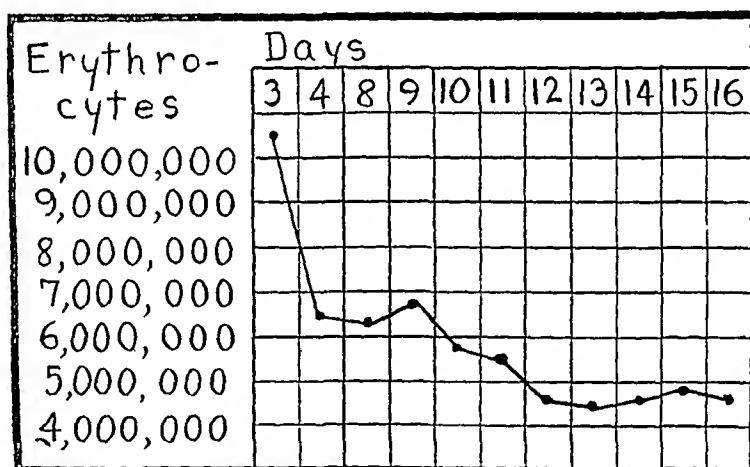
* From the service of Dr. Charles H. Nielson, Department of Internal Medicine, St. Louis University School of Medicine, St. Louis City Hospital.

REPORT OF CASE

G. L., a colored man, aged 22, entered the hospital on the morning of Nov. 29, 1916. He was conscious and rational; his pulse was of fairly good volume, and he did not appear to be in immediate danger. He said he had taken two teaspoonfuls of tincture of cantharides by mistake about two hours prior to his admission.

On examination his pupils were found dilated, regular, equal, and reacting both to light and distance. No eschars were present in his mouth or on his tongue, but his throat was reddened. His heart and lungs appeared normal, his abdomen was rigid, and he was tender in the region of the epigastrium. His deep reflexes and knee jerks were exaggerated.

At 7 p. m. he was very restless and complained of strangury and of severe pain over the kidneys. There was much blood in his urine. Dry cups were applied to the lumbar region for thirty minutes without affording relief, but morphin (0.25 grain) given hypodermatically, quieted him somewhat. His blood pressure at this time was systolic 130 mm. and diastolic 70 mm. His white blood count was 19,000. In addition to the other signs and symptoms men-



Curve showing effect on the erythrocytes of cantharides poisoning.

tioned he soon began vomiting everything immediately after swallowing and complained of substernal and epigastric pain on taking solids and liquids. He suffered constant pain posteriorly over his kidneys and passed a bright red urine. Intense pain in the scrotum was caused by the passage of blood.

The patient was able to sleep but little on account of the pain in the back, which was only relieved by large doses of morphin. Extreme general hyper-tonus of all the muscles and moderate priapism were present.

December 1. His urine was still very bloody, the microscopic field consisting almost entirely of red blood cells. The collected twenty-four hour quantity of urine amounted to 2,600 c.c. The erythrocyte count was 10,430,000; the leukocyte count, 24,000; hemoglobin, 80 per cent. (Tallqvist).

December 2. Erythrocytes, 6,430,000; leukocytes, 22,000.

December 3. Pain in the back continues intense, hematuria persists; twenty-four hour specimen of urine, 1,600 c.c.

December 4. Twenty-four hour specimen of urine, 1,800 c.c. There is occult blood in the stool; no edema present.

December 5. The patient was placed on a nonprotein diet and fluid intake limited to 1,500 c.c. daily. Blood pressure, systolic 132; diastolic 80.

December 6. Blood pressure, systolic 120, diastolic 80. Twenty-four hour specimen of urine, 1,200 c.c. There is no decrease in hematuria. Erythrocyte count, 6, 216,000.

December 7. The patient feels better, hematuria is less marked. Twenty-four hour specimen of urine, 600 c.c. Blood pressure, systolic 110, diastolic 78. Erythrocytes, 6,760,000; leukocytes, 19,000.

December 8. The patient is fairly comfortable; hematuria is diminishing. Twenty-four hour specimen of urine, 780 c.c. Blood pressure, systolic 114, diastolic 76. Erythrocytes 5,920,000; leukocytes 20,000.

December 9. The patient is improving. Blood pressure, systolic 105, diastolic 75. Twenty-four hour specimen of urine, 1,400 c.c. Erythrocytes 5,550,000; leukocytes 12,000.

December 10. Erythrocytes 4,690,000; leukocytes 10,200. Patient was placed on soft diet.

December 11. Urine, lemon colored, showing very few leukocytes. Albumin decidedly decreased. Twenty-four hour specimen of urine, 1,820 c.c. Erythrocytes, 4,670,000; leukocytes, 9,700.

December 12. Following fresh fruit, eaten the previous day and the administration of alkalies, his urine again became red. Many erythrocytes were found microscopically. Twenty-four hour specimen of urine, 1,150 c.c. Erythrocyte count, 4,800,000; leukocyte count, 9,800.

December 13. The patient is improving; the urine is clear with very few red blood cells. Erythrocyte count, 4,900,000; leukocyte count, 9,100.

December 17. Patient is in good condition. Phenolsulphonephthalein appeared in the urine nine minutes after injection; 38 per cent. was eliminated the first hour; 25 per cent. the second hour. The urine is clear, lemon colored, specific gravity 1.009. No albumin, sugar, casts or blood cells found. Erythrocyte count, 4,780,000; leukocytes, 8,800; hemoglobin, 70 per cent. Blood pressure, systolic 104, diastolic 64. The patient lost 7 pounds during his illness.

COMMENT

The patient's temperature was subnormal in the beginning but later became normal. There was slight acceleration in the pulse rate. There were no ocular findings and the Wassermann was negative. He was discharged December 18, in good condition, twenty days after admission.

THE EFFECT OF PANCREATECTOMY ON THE CATALASE CONTENT OF THE TISSUES *

J. KENNEDY, A.B.

Laboratory of Physiological Chemistry, University of Illinois Medical School
CHICAGO

AND

W. E. BURGE, A.B., A.M., PH.D.

Physiological Laboratory of the University of Illinois
URBANA, ILL.

Of the older workers who recognized the coincidence of diabetic symptoms and lesions of the pancreas, the names of Cowley (1788), Bright, Lloyd and Elliotson (1833) and Bouchardat (1883) may be mentioned. Von Mering and Minkowski¹ (1889), however, were the first to show that complete pancreatectomy invariably resulted in severe diabetes. Much work has been done and several theories have been advanced in an attempt to explain the fact that when the pancreas is extirpated the animal loses the power of burning carbohydrates. The literature on the subject is so enormous that no attempt will be made to review it. A fairly complete and exhaustive review is made by Allen,² and by Lusk.³ In very severe cases of diabetes the body is not only unable to burn sugar, but is able to burn fat only as far as beta-oxybutyric acid, and as for the protein, a part of its amino-acids are converted into sugar and a part into beta-oxybutyric acid, neither of which the animal is able to burn.⁴ It should be kept in mind, however, that while oxidation is imperfect or defective in diabetes, it is not decreased, but is rather increased, as is indicated by the increased heat production.⁵ The present investigation was begun in an attempt to find an explanation for the defective or imperfect oxidation in diabetes.

We⁶ have found that the amount of oxidation in the different muscles is directly proportional to the amount of catalase; that by increasing or decreasing the amount of work, and hence oxidation in

* Submitted for publication Aug. 21, 1917.

1. Von Mering and Minkowski: *Diabetes mellitus nach Pancreasextirpation*. Arch. f. exper. Path. u. Pharmacol., 1889-1890, **26**, 371.

2. Allen, F. M.: *Glycosuria and Diabetes*, 1913.

3. Lusk, Graham: *The Science of Nutrition*, 1917.

4. Magnus-Levy: *Ergebn. d. inn. Med.*, 1908, **1**, 404.

5. Pettenkofer and Voit: *Ztschr. f. Biol.*, 1867, **3**, 380. DuBois and Veeder: *THE ARCHIVES INT. MED.*, 1910, **5**, 37.

6. *Am. Jour. Physiol.*, 1916, **41**, No. 2; 1917, **42**, No. 3; 1917, **43**, No. 1; 1917, **43**, No. 3; 1917, **43**, No. 4.

a muscle, there was a corresponding increase or decrease in the catalase content; that in thyroid feeding, where oxidation is increased, there was a corresponding increase in the catalase of the blood; that in phosphorous poisoning, where oxidation is defective, the catalase of all the tissues was decreased, being most marked in the liver; that in starvation, where oxidation is decreased in the less vital tissues and remains normally high in a vital organ such as the heart, there was a corresponding decrease in the catalase content of the less vital tissues, while it remained normally high in the heart. Since in all the instances cited where oxidation is increased or decreased, or rendered defective, there was a corresponding increase or decrease in catalase, the conclusion was drawn that there exists a very close relationship between catalase content and amount of oxidation. It may be that oxidation in the tissues is brought about by catalase by the liberation of atomic oxygen from an organic peroxid comparable in structure to hydrogen peroxid, as was suggested by Bach and Chodat. However this may be, one is unable to say at present; yet if it can be shown that the catalase of the tissues is decreased in diabetes, it would be another instance in which catalase is decreased when oxidation is rendered defective, and there may exist a causal relationship between the decreased catalase and defective oxidation.

The animals used in the present investigation were dogs. Several of these animals were depancreatized.⁷ Examination of the urine on the first day after the operation showed the presence of sugar in all the depancreatized animals. The longest time any animal was permitted to live after the operation was thirteen days, while the shortest was six days. Those that had gone thirteen days were in very bad condition and showed large amounts of sugar in the urine. After the animals were etherized their blood vessels were washed with large quantities of 0.9 per cent. sodium chlorid until free of blood, as was indicated by the fact that the wash water gave no test for catalase. The bloodless liver and heart were then removed and ground up separately in a hashing machine.

The catalase content of the heart was determined by adding 1 gm. of the ground material to 45 c.c. of hydrogen peroxid at 27 C., while 1 gm. of the liver was added to 500 c.c. of hydrogen peroxid in a bottle. A greater amount of hydrogen peroxid was used for the liver because of the greater catalase content of this organ. As the oxygen gas was liberated by the heart muscle, it was conducted through a rubber tube to an inverted buret previously filled with water, and that liberated by the liver to a large, inverted, graduated cylinder. The amount of oxygen gas liberated by the heart and liver, respectively, was read off directly from the buret and cylinder where it had displaced the water. After this volume was reduced to standard atmospheric pressure the resulting volume was taken as a measure of the amount of catalase in the ground material. A full description of the method may be found in a previous publication.

The results of the determinations are given in the accompanying table. It will be seen that the average amount of oxygen liberated by

7. We are indebted to Dr. W. F. Petersen of the University of Illinois Medical School for depancreatizing the animals.

1 gm. of the liver of the normal dogs in ten minutes from 500 c.c. of hydrogen peroxid was 466 c.c., while that liberated by the liver of the diabetic animals was only 130 c.c. The average amount of oxygen liberated by 1 gm. of the heart of the normal dogs in ten minutes from 45 c.c. of hydrogen peroxid was 48 c.c., while that of the heart of the diabetic dogs was 25 c.c. By comparing the data from the normal animals with that from the diabetic animals it will be seen that the catalase content of the livers of the diabetic animals was decreased 72 per cent., and that the catalase content of the heart was decreased 48 per cent.

Two dogs were used three days after being depancreatized. These showed a decrease in the catalase of the liver and heart, but not to such a great extent as those that had been depancreatized for longer periods.

TABLE OF CATALASE DETERMINATIONS IN NORMAL
AND DIABETIC LIVER AND HEART

Tissue	Dog	Dog	Dog	Dog	Dog	Average Amount of Oxygen in C.c.	Percentage Decrease
Liver	1	2	3	4	5		
Normal*	440	575	390	425	500	466	
Diabetic	125	140	88	175	120	130	72
Heart							
Normal	52	56	48	42	44	48	
Diabetic	24	25	34	22	22	25	48

* After "normal" and "diabetic" are given the number of cubic centimeters of oxygen liberated in ten minutes from hydrogen peroxid by 1 gm. of the liver and of the heart of normal and of diabetic dogs. Dog 1 was diabetic for six days; Dog 2 for seven days; Dog 3 for nine days, and Dogs 4 and 5 for thirteen days.

From the preceding observations it would seem that the catalase of the tissues of depancreatized dogs decreases during the first five or six days, at which time a certain low level is reached and maintained. Verzar⁸ found that the dog does not completely lose its power of oxidizing glucose until the fourth day after pancreatectomy; hence it would seem that the power of the diabetic dog to burn glucose decreases parallel with the decrease in the catalase content of the tissues.

We have presented evidence showing that catalase is formed in the liver, and that this is normally given off to the blood as a result of stimuli received over the splanchnics. We found, for example, that when a cat was enclosed in a small cage and a dog on the outside of the cage was permitted to bark and bite at the cat, and as a result the cat fought back at the dog, the catalase of the liver of the cat was very greatly increased. From these and similar experiments the conclusion was drawn that the great physical exertion put forth in times of

8. Verzar: *Biochem. Ztschr.*, 1914, 66, 75.

stress and combat is made possible by the increased output of catalase from the liver into the blood, and that this is carried to the muscles where it augments oxidation, thus supplying the increased energy for the fight. The decreased supply and constant destruction of the catalase is probably responsible for the decreased catalase in the tissues of diabetic animals. Given the decreased catalase content of the tissues in diabetes, the characteristic imperfect or defective oxidation in this disease naturally follows if catalase is the enzyme principally responsible for oxidation. The question that naturally arises in this connection is, how does the extirpation of the pancreas decrease the catalase of the tissues? The explanation that suggests itself is that the pancreas gives off an internal secretion, which is carried to the liver and increases the formation of catalase in this organ. The fact that the liver gives up its glycogen after pancreatectomy,¹ and that it seems to lose its power of forming glycogen from most sugars⁹ would also seem to indicate a regulatory action on the part of the secretion of the pancreas. The observations of De Meyer¹⁰ would seem to offer still further evidence in this direction. This observer found that the liver when perfused with Ringer's solution lost less glycogen if pancreatic extract was added, and that if the liver came from a depancreatized animal its function of storing glycogen could be restored by the addition of pancreatic extract to the perfusing fluid.

SUMMARY

Extirpation of the pancreas decreases the catalase content of the liver by about 75 per cent., which results in the decreased output of catalase into the blood and hence a lessened supply to the tissues.

The decreased catalase content of the tissues may account for the imperfect or defective oxidation in diabetes, since the amount and intensity of oxidation is so inseparably linked with catalase.

9. Epstein and Baehr: *Jour. Biol. Chem.*, 1916, **24**, 1.

10. DeMeyer, J.: *Sur les relations entre la secretion interne du pancreas et la fonction glycogenique du foie. Arch. internat. de physiol.*, 1910, **9**, 1 to 100.

THE IRON METABOLISM OF HEMOCHROMATOSIS *

C. P. HOWARD, M.D., AND F. A. STEVENS, M.D.

IOWA CITY, IOWA

The object of our study was to investigate by modern chemical and metabolic methods the iron and its associated metabolism in a typical case of hemochromatosis. In spite of the fact that there are now in the literature some seventy-two cases, nine¹ of which have been reported since T. P. Sprunt's² excellent paper in 1911, only one attempt has been made to investigate the iron metabolism.

Garrod³ and his co-workers in 1914 published some results of their clinical and chemical studies in a typical case of hemochromatosis. Their work is, however, open to criticism and will be dealt with subsequent to our own clinical and chemical findings.

AUTHORS' OBSERVATIONS

The medical history and postmortem findings of our patient are as follows:

Clinical Summary: Irishman, aged 54. In 1914 pigmentation of the skin; in 1916 enlargement of the liver and in 1917 glycosuria. Diagnosis of hemochromatosis confirmed by examination of the skin. Death three years after onset of disease. Necropsy.

History.—W. F. (Clinical No. 3283), aged 54, a carpenter, was referred by Dr. C. G. Beveridge, Muscatine, Iowa. He was admitted Jan. 8, 1917, complaining of weakness.

Family History.—His mother died from gallstones and an obscure liver trouble. One sister, the patient believes, has trouble similar to his own. There is no other history of importance in the family. The patient's wife has had two full term children and no miscarriages.

Personal History.—The patient was born in Iowa of Irish parents. He has been a carpenter by trade. Uses some tobacco and admits an occasional glass of alcoholics, but never to excess. Denies absolutely syphilis, but admits

* Submitted for publication July 12, 1917.

* From the Medical Clinic and Chemical Research Laboratory of the University Hospital, State University of Iowa.

1. Potter, N. B., and Milne, L. S.: Am. Jour. Med. Sc., 1912, **143**, 46. Vanderhoef, D., and Hutcheson, J. M.: Old Dominion Jour. Med. and Surg., 1912, **15**, 1. Blumer, G.: Yale Med. Jour., 1912, **18**, 190. Labbe, M.: Arch. de mal. de l'appar. digest., 1912, **6**, 403. Gaskell, J. F., Mackenzie, Wallis R. L., Sladen, A. F., Vaile, P. T., and Garrod, A. E.: Quart. Jour. Med., 1913-1914, **7**, 129. Fiessinger, N., and Laurent, L.: Ann. de méd., 1914-1915, **2**, 129. Muir, R., and Dunn, J. S.: Jour. Path. and Bacteriol., 1914-1915, **19**, 226. Roth, O.: Deutsch. Arch. f. klin. Med., 1915, **118**, 224. McCreery, A. H.: Canad. Med. Assn. Jour., 1917, **7**, 481.

2. Sprunt, T. P.: Hemochromatosis, THE ARCHIVES INT. MED., 1911, **8**, 75.

3. Gaskell, J. F., Mackenzie, Wallis R. L., Sladen, A. F., Vaile, P. T., and Garrod, A. E.: Quart. Jour. Med., 1913-1914, **7**, 129.

gonorrhea at 20. He had the ordinary diseases of childhood—measles, mumps and chickenpox. He also was subject to chills and fever when living on the Mississippi as a boy. When 8 years old he had a fever which lasted three weeks and which was accompanied by delirium, but terminated suddenly with a profuse sweat; this was considered typhoid. He has been subject to winter colds all his life, but denies bronchitis, pleurisy and pneumonia, hemoptysis and night sweats. There was no dyspnea, palpitation or edema. His appetite has always been good; he has no dyspnea, gaseous eructations or pain after eating; no nausea or vomiting. The bowels are inclined to constipation. There was no melena, hemorrhoids, jaundice, etc., before the present illness. Micturition is normal, both as to amount and frequency. Admits impotence for the past fourteen years.

The patient denies nose or throat affections until March, 1915, when he had pain and swelling of the left side of the face for which four teeth were extracted and an antromental operation was performed following a diagnosis of empyema of the maxillary antrum. The condition rapidly cleared up though he dates most of his marked symptoms from this infection.

Present Illness.—While he dates the onset of his present illness from the empyema of the antrum in March, 1915, he admits that his friends and family have noticed a peculiar color to his skin for three or four years and that some time prior to examination he thought the liver was enlarged. He felt perfectly well, however, until the aforementioned infection, which resulted in marked weakness and a loss of 20 pounds in weight, which he has never regained.

About January, 1916, he was told by a physician that the liver was enlarged. He kept at work all the year except for a few weeks in the summer of 1916 when he found the heat unbearable and he became weak and a little short of breath and developed a slight edema of the right shin. The urine was repeatedly examined during these months, but was always said to be normal. Suddenly, Dec. 25, 1916, he developed polyuria and Jan. 6, 1917, the urine was said to contain sugar. The bowels, if anything, had been more constipated than previously. The patient had kept at work up to the date of admission and he entered the hospital because of an opportune holiday.

Physical Examination.—Examination made by Dr. C. P. Howard Jan. 9, 1917. The patient is a poorly nourished, white man aged about 50; he lies comfortably in bed and does not look sick. The color is peculiar. The skin of the face, trunk and extremities has a muddy appearance, with a slightly bronzed hue. The lips and ears are ruddy, almost cyanosed, forming a striking contrast to the face. There is, however, no special pigmentation of the skin of the axillae, groins and areolae. There is a distinct and somewhat diffuse pigmentation over the shins. The skin is dry and strikingly free from hair, there being no visible hair over the trunk or in the axillae. Pubic hair is very sparse. The thighs and shins have no hair. The scalp is covered by a growth of fine black hair turning gray. The eyelashes are heavy. He has a rather light beard and moustache. The mucous membrane of the mouth is injected but presents no pigmentation. On the soft palate is a small telangiectasis. Many teeth are missing, necessitating a plate in the upper jaw; the other teeth are carious. The tongue is straight, moist and slightly coated; on the under surface there are a few small telangiectases. The sclerae are muddy but not definitely bile stained. The conjunctivae show marked injection promptly to light. Lymph glands are nowhere palpable.

The thorax is symmetrical and somewhat barrel shaped. The lungs are clear on percussion and auscultation. Heart: Point of maximum intensity is in the fifth intercostal space 8 cm. from the midsternum, relative cardiac dullness begins above at third rib and extends 3.5 cm. to right and 9 cm. to left. Sounds are regular and clear; no murmurs. The aortic second sound is louder than the pulmonic second. Pulse: 100, large, regular in force and rhythm. The radial wall is uniformly thickened. Blood pressure, systolic, 124; diastolic, 80.

The abdomen is rounded but reveals no enlarged veins; the umbilicus is depressed. The walls are soft and doughy. There is no dulness in the flanks; no signs of fluid. The edge of the liver is readily felt two fingers' breadth below the costal margin. The edge is rounded and firm, the surface rough and nodular. The upper border of liver dulness begins at the fifth rib and extends vertically 17.5 or 4.5 cm. below the costal margin in the right parasternal line. The left lobe can be traced across the epigastrium to the costal border of the left side. The spleen itself cannot be felt in its usual location, but on deep palpation a firm mass can be felt well under the costal border which is no doubt the spleen. Splenic dulness does not seem increased. There are no epigastric masses to be felt. The tendon and plantar reflexes are normal throughout. Pallesthesia of the right shin, 100 per cent.; left shin, 100 per cent. Touch and pain are intact throughout.

The muscles are small and though they show no localized atrophy or degeneration there is a marked myoidema. All muscle groups seem fairly strong (70 per cent. of normal).

The external genitalia are rather small but symmetrical.

Rectal examination reveals a great deal of fulness of the hemorrhoidal veins; the middle lobe of the prostate is smooth and not tender.

A clinical diagnosis of hemochromatosis was further suggested by the presence of a slight but constant glycosuria.

Jan. 11, 1917, a small piece of skin was removed for histologic study, but through an error was fixed in Zenker's fluid and consequently the abundant yellowish-brown pigment found in the corium did not give the iron reaction.

January 25, a second portion of the skin was removed and fixed in formaldehyd solution and this time Dr. C. E. Royce obtained the characteristic iron reaction with potassium ferrocyanid.

The Urine: The patient was first placed on a general diet (hospital light) for the first two days. During this time he voided from 425 to 2,075 c.c. in the twenty-four hours, which contained 1.46 to 4 per cent., or from 6.2 to 83 gm. of glucose. It was free from acetone and diacetic acid and negative for albumin and casts.

He was then starved for twenty-four hours, when he became sugar-free and showed no evidence of acidosis. His tolerance was determined in the usual manner advised by Allen and Joslin. His final diet consisted of 90 gm. of carbohydrates, 65 gm. of protein and 120 gm. of fat. This gave him sufficient calories for his weight and was well tolerated by the patient up to February 5, the date of his discharge, when he was sugar-free and acetone-free.

His weight on admission was 126 pounds, and on discharge 125 pounds.

From Jan. 22, 1917, to Feb. 1, 1917, he was on special diet in the metabolism ward for the study of his iron metabolism. This had no apparent effect on his glycosuria or acidosis.

Blood: Jan. 8, 1917. Hemoglobin, 100 per cent. (Sahli, corrected); red blood cells, 4,280,000; white blood cells, 8,680. Smears revealed normal red cells. The differential count gave: polymorphonuclears, 55 per cent.; lymphocytes, 33 per cent.; transitionals, 8 per cent.; large mononuclears, 1 per cent.; eosinophils, 3 per cent.

Jan. 9, 1917. Blood sugar, 0.23 per cent.; serum was negative for urobilin and urobilinogen; no bile pigments or acids were found on dialysis; calcium content of blood, 9 mg.

Jan. 13, 1917. The Wassermann reaction on blood serum was negative.

Jan. 16, 1917. Fragility test: hemolysis begins at 0.36 and is complete at 0.30.

Gastric Contents: Jan. 9, 1917, Ewald test breakfast; removed in forty minutes; amount, 270 c.c.; consistence and color normal. Total acidity, 8; free hydrochloric acid, 5; Meyer's test negative. Microscopic test negative.

Duodenal Contents: Removed by Einhorn bucket. After one and a half hours bile-stained fluid escaped freely from the tube; color, clear golden

HEMOCHROMATOSIS

R, 1917

yellow; reaction, neutral to litmus; total acidity = 5; free hydrochloric acid = 0; bile present; protease = 2; amylase = 100; lipase = 0; blood was negative to Meyers' test; urobilin negative or \pm ; urobilinogen, negative; microscopically negative.

Urobilin and Urobilinogen: On admission the urine was negative for the urobilinogen reaction and the duodenal contents removed by the Einhorn tube gave only a trace of urobilin and no urobilinogen.

TABLE 1.—UROBILIN AND UROBILINOGEN

First Period	Jan. 23	Jan. 24	Jan. 25	Jan. 26	Jan. 27	Total
Urine.....	2,255	1,448	1,740	1,500	2,100	8,743
Feces.....	4,375		120,000			124,375

Daily = 26,634 dilutions.

		Feb. 3	Feb. 4	Total
Urine..... Second Period	1,700 Feb. 2	2,700	600	5,000
Feces.....	3,500	38,000		41,500

Daily = 15,520 dilutions.

A subsequent quantitative determination of these in the urine and stools was made by the Wilbur and Addis method⁴ (spectroscopic extinction method) and a well marked increase was found in both, averaging daily 26,634 dilutions and at a later period 15,520 (instead of the normal 5,000 to 8,000).

TABLE 2.—IRON METABOLISM (IN MILLIGRAMS OF IRON)

	Jan. 23	Jan. 24	Jan. 25	Jan. 26	Jan. 27	Total
Intake.....	6.1	6.1	5.7	5.7	5.7	29.3
Urine.....	0	0	0	0	0	0
Feces.....	5.0		21.8			26.8

Balance +2.5

January 28, wholeblood = 45 mg. per cent.

Iron Metabolism: Jan. 23, 1917, the patient was placed on a weighed and measured diet of agar, milk, eggs and salt with especial view to the study of the iron metabolism. The intake of iron as determined by Neumann's method for the five-day period equaled 29.3 mg. For this period there was no iron in the urine and only 26.8 mg. in the feces; that is to say, a retention of 2.5 mg. in the five days.

4. Wilbur, R. L., and Addis, T.: Urobilin; Its Clinical Significance, THE ARCHIVES INT. MED., 1914, 13, 235.

At the end of the period the iron content of the whole blood was determined by Neumann's method and found to be 45 mg per 100.

Nitrogen balance was determined, first, as a check on the whole experiment, and secondly, to be sure that our patient was in metabolic equilibrium.

The nitrogen intake was 42.5 gm. and the output 42.16 for the five-day period (Table 3).

TABLE 3.—TOTAL NITROGEN

Intake		Output	
		Urine	Feces
January 23	8.5	7.25	0.6
January 24	8.5	7.2	0.63
January 25	8.5	7.4	
January 26	8.5	8.5	
January 27	8.5	8.9	2.28
Total	42.5	39.25	2.91 Bal. + 0.34

Nitrogen Partition of Urine

	Total	NH ₃ N.	Urea N.	Uric Acid N.	Orentinin	Creatin	Undetermined N., per Cent.
January 23	7.25	0.51 = 7.03 %	5.84 = 80.55 %	0.183 = 2.52 %	0.466 = 6.43 %	0.057 = 0.08 %	3.89
January 24	7.2	0.59 = 8.20 %	6.09 = 84.61 %	0.136 = 1.88 %	0.335 = 4.65 %	0.032 = 0.045 %	0.72
January 25	7.4	0.50 = 6.75 %	6.50 = 87.83 %	0.10 = 1.35 %	0.277 = 3.74 %	0	0.33
January 26	8.5	0.50 = 5.88 %	7.10 = 83.53 %	0.17 = 2.00 %	0.263 = 3.09 %	0	5.50
January 27	8.9	0.60 = 6.74 %	7.78 = 86.80 %	0.152 = 1.70 %	0.269 = 3.02 %	0	1.74

TABLE 4.—SULPHUR METABOLISM

Date	Intake	Output in Urine	Total Sulphur in Feces	Neutral	Ethereal	Inorganic
January 23.....	0.623	0.2747	—			
January 24.....	0.623	0.4460	0.0826			
January 25.....	0.623	0.3328				
January 26.....	0.623	0.4642	0.4480	0.0263 = 5.6%	0.0155 = 3.3%	0.4224 = 91.1%
January 27.....	0.623	0.4179	0.0205 = 5%	0.011 = 2.5%	0.3864 = 92.5%
Total.....	3.115	1.9336	0.5308			

Balance +0.6506.

The nitrogen partition in the urine was normal.

The sulphur metabolism was next determined (Table 4). It was found that in a five-day period there was a retention of sulphur amounting to 0.6506 gm., or an average daily retention of 0.1301 gm. sulphur. The sulphur partition of the urine was normal.

The phenols were studied by the Folin and Denis colorimetric method⁵ because of the possibility that an injured liver cannot conjugate or detoxicate these bodies. In our case there is a normal ratio between the combined and total phenols (Table 5).

TABLE 5.—PHENOLS

	Jan. 23	Jan. 24	Jan. 25	Jan. 26	Jan. 27
Free, gm.	0.443	0.390	0.365	0.342	0.358
Total, gm.	0.618	0.650	0.559	0.661	0.594

As the patient was anxious to leave the hospital he was discharged Feb. 5, 1917.

Two days later, though apparently adhering to his diet, he suddenly developed severe abdominal pain, nausea and vomiting, fever, delirium, air hunger and coma. Death occurred at 12 noon, February 7, a little less than forty-eight hours after leaving the hospital.

Thanks to the courtesy of the home physician, Dr. C. G. Beveridge, permission for a necropsy was obtained, and was performed Feb. 8, 1917, by Dr. C. E. Royce, the hospital pathologist.

Necropsy.—Anatomic. Diagnosis: Hemochromatosis. Cirrhosis of liver, pancreas and spleen. Hypertrophy of the retroperitoneal lymph nodes of the upper abdomen. Chronic adhesive pleuritis (bilateral). Chronic adhesive peritonitis about the liver. Atrophy of the testicles. Brown atrophy of the heart muscle.

The body is that of an adult white male without deformity, but emaciated. The skin over the whole body is of a faint grayish-brown color, but this is especially well marked over the face and hands. There are no superficial lesions. The superficial lymphatics, including both epitrochlear nodes, are palpable, but not enlarged. The subcutaneous fat is thin, and bright yellow. The pectoral muscles are pale red, with a brownish tinge. The omentum is thin and contains very little fat. The abdominal cavity shows no adhesions except over the dome of the liver on the right side, and between the gallbladder and transverse colon.

The abdominal cavity contains a large amount of embalming fluid. The left pleural cavity shows no fluid, but presents dense adhesions laterally and posteriorly over the diaphragm. The right pleural cavity shows no fluid, but presents adhesions over the outer, posterior and lower margins of the lower lobe. The pericardial cavity presents no adhesions, but shows about 50 c.c. of blood-tinged opaque fluid. The mesenteric vessels show no thickening or evidence of hemorrhage. The mesenteric nodes are not enlarged. The intestines are very friable. The appendix presents a constriction at its base.

The liver is unusually large. Owing to lack of facilities its weight and measurements were not taken. The surface is rough and pebbled and the consistence is hard and leathery. The cut surface of the liver presents an appear-

5. Folin, O., and Denis, W.: Jour. Biol. Chem., 1915, 22, 305.

ance like that of a crushed stone floor, in which fine rusty brown opaque particles are imbedded in a gray translucent substance. These opaque patches vary from 0.5 mm. to 1 mm. in diameter. In some places the liver tissue is softer than in others, and here the tissue seems to be honeycombed by numbers of small spaces. The gallbladder is thin walled and contains dark green bile, but no stones.

The spleen is larger than usual. Its contour is irregular and its surface smooth. The outer surface is gray in color. The cut surface is dark red and the consistence friable.

The pancreas is smaller than usual and very flabby in consistence. Its color in general is a chocolate brown. Along the body of the pancreas and about the head are enlarged lymph nodes which are rusty brown in color, both on the exterior and on the cut surface.

The adrenals are very small. The consistence is that usually found. The relation of the cortex to the medulla is that usually seen.

The kidneys present about the same general appearance. The outer surface is reddish-brown, and smooth. The capsule strips easily. The cut surface of the kidney is dark red tinged with brown. The consistence is rather flabby. The right kidney shows a 1 cm. cyst on the posterior surface near the hilum.

The right lung is large and crepitant. The upper and middle lobes are gray. The lower lobe is reddish-gray. The cut surface is bright red on the lower lobe. The cut surface of the upper and middle lobes are gray. The left lung is large and crepitant. The upper lobe is gray within and without. Scattered through the upper and lower lobes are small calcareous nodules. The apex shows scar formation.

The heart is of the usual size. The muscle is reddish brown. The valves are intact, although the aortic and mitral valves are somewhat thickened. The aorta is marked by a thickening of its wall and a few calcareous plaques on its intima.

The bladder is small and the wall moderately thick. The inner surface is pale and not roughened, and shows no areas of reddening.

The prostate gland is small and firmly elastic in consistence. The testicles are flabby. The tubules do not unravel readily, breaking easily.

The thyroid gland is small, firm and reddish brown in color.

Microscopic Examination.—A section from the liver shows a remarkable condition in which the amount of fibrous tissue present far exceeds the amount of parenchyma. The parenchyma which is present appears in irregular oval-shaped areas and many such areas are seen in which a large part of the liver tissue has disappeared, leaving a hole. In such clumps many of the corners of the liver cells are missing, so that they appear roughly circular or oval. The nuclei stain indistinctly and the whole picture is obscured by masses of brown granules, which occupy the cells, crowding many of them to the limit. Brown granules are not found between the cells. The intervening tissue is dense and fibrous and in it appear structures having all the appearance of bile ducts. There are also scattered through the fibrous tissue many small mononuclear leukocytes. Granules are present in the fibrous tissue but are not as numerous as in the clumps of the liver cells. The granules may be found to some extent apparently free in fibrous tissue, but in the structures, which appear like bile ducts, the granules are very numerous and intracellular. Sections of the liver stained by Nishimura's method to demonstrate the reaction for iron of the blood pigment show that all the brown granules react with the combination of ammonium sulphid, potassium ferrocyanid and hydrochloric acid, giving a prussian blue color.

The pancreas has the usual appearance greatly altered by extensive atrophy of its parenchyma cells. Its group of cells contain heavy deposits of brown granules. There is no evidence of the formation of cells into acini, the scattered cells being found in a loose network of connective tissue. The islands of Langerhans are no longer to be identified as such. The epithelium of the

ducts has desquamated and may be found in the lumen mingled with cellular and amorphous debris.

The spleen has its usual appearance altered by the thickness of its trabeculae, and enormous density of its finer reticulum so that a large part of the pulp appears to be made up of younger connective tissue cells. The splenic corpuscles are present and have their usual appearance. Enormous numbers of red blood cells crowd the blood spaces.

The general appearance of the kidney section is changed by many definite hemorrhages into the tissue, especially in the cortex. The tubular epithelium does not take a differential stain, in most places the nucleus being indistinguishable from cytoplasm. The general shape of the tubules is preserved. The glomeruli show capsules of the usual thickness. The capillaries are enormously distended with red blood cells and in some places the endothelium of the tufts appears to be proliferated. There is infiltration of the tissue by leukocytes, and congestion of all its vessels.

The adrenal glands are in a fair stage of preservation. The cells show good differential staining. The blood vessels of the medulla are distended with red blood cells, some of them to the point of rupture. The peculiar characteristic of the section is that the cells of the glomerular zone are in large part packed with brown granules. The cells so affected are those just beneath the capsule. Very few if any granules are found in the other cells shown in the section.

The section from the lymph node found near the head of the pancreas shows a loosely arranged structure in which lymph follicles are abundant and in their usual arrangement. In the lymph spaces are large numbers of cells. They are oval in shape, having the general appearance of endothelial cells. These are loaded with brown granules in lesser number than may be found throughout the section. There are also giant cells of the so-called foreign body type. These giant cells almost invariably contain material having a somewhat crystalline appearance and varying in color from light yellow to black. The material is arranged in the form of large and small masses having shapes varying from circular to fusiform. Regardless of the shape or color of these patches, they are highly refractile, appearing like huge granules found in the endothelial cells. The section of the lymph node treated to show the reaction for iron shows the endothelial cells to be loaded with prussian blue, and these large masses of pigment found in the giant cells are very dark blue. A slight reaction is seen also in the connective tissue cells of the fibrous frame work. The lymphoid cells, however, appear to be free.

The lungs show a moderate amount of congestion. The walls of the air sacs are slightly thickened and some of the vesicles contain serum and a few leukocytes. Definite black pigment is found in some of the thicker septa. In the other places the pigment reacts with the chemicals used, giving a bluish black appearance.

The cross striations of the heart muscle are fairly well preserved. The nuclei are for the most part swollen and present at their poles numbers of yellowish brown granules. There is no increase of interstitial tissue and blood cells do not appear engorged. Sections of the heart muscle treated to show the iron reaction show that all the fibers present at some point granules of prussian blue; these become more numerous near the nuclei. In some places the muscle fiber seems to have disappeared leaving its sheath within which may be seen a few dense masses of pigment.

Section of the testicle shows the tunica thick and dense. The gland tissue is also dense through an overgrowth of the intertubular tissue. The tubules are all atrophic and show little if any appearance of a lumen. What epithelial cells remain are small, being represented mainly by their nuclei. Pigment is present in some of the connective tissue and in the walls of some of the tubules. It is also present to some extent in the walls of the blood vessels. This amount is negligible in comparison with quantities found in the other organs.

The prostate gland presents about the usual proportion between the fibrous and glandular tissue. The epithelium lining the gland spaces is, however, thin and atrophic in places. There is no evidence of congestion or inflammatory change. Occasionally pigment deposits may be seen in the walls of the gland spaces and in some of the connective tissue cells. This amount is very small, however.

In the kidney the deposits of pigment appear almost entirely limited to the portion of the tubules in the cortex. The amount of pigment found in the kidney is small compared with that seen in the other organs, or with that seen in the kidney of pernicious anemia. Examination with the higher powers shows pigment present in the glomeruli.

The Iron Content of the Viscera.—Portions of the liver, spleen, pancreas and kidneys were dried to constant weight and the iron content determined by Neumann's method.⁶ This method gave uniform results. Unfortunately, owing to the fact that the necropsy was performed in another town and after the body had been embalmed, the fresh weights of the various viscera were not available and we have had to content ourselves with the amount of iron per 100 gm. of dried substance, and of course cannot give the total iron content of each viscus. These figures are tabulated (Table 6) with those of other authors for the sake of comparison. It will be immediately seen that in our case there was an enormous retention of iron in the retroperitoneal lymph glands⁷ (4.2 per cent.), liver (3.09 per cent.) and a considerable one in the pancreas (1.439 per cent.), while that of the spleen (0.825 per cent.) and the kidneys (0.406 per cent.), though more than in the normal and certain diseased conditions, was relatively much less.

While many other authors (Quincke, Auscher and Lopicque, Jeanselme and Garrod) have determined the iron content of the liver, at least, they have expressed it in percentages of the fresh organs; and though a rough estimate in dried weight may be obtained by multiplying the moist weight results by six, we do not consider these figures sufficiently accurate for comparison with ours and the others given in our table.

Further, in only a few cases has the iron been determined in the spleen, pancreas and kidneys and retroperitoneal lymph glands. For comparison we also tabulate some figures in Addison's disease, pernicious anemia, cirrhosis of the liver and acute myelocytic leukemia.

DISCUSSION OF IRON METABOLISM

Time and space will not permit us to enter into a general discussion of the pathogenesis of hemochromatosis. The reader is referred to the papers of Anschütz,⁸ Fitcher,⁹ Sprunt² and McCreery¹⁰ for a review of the cases in the literature and a criticism of the various theories held. Almost every writer seems to have added something to the confusion of our knowledge of the pathogenesis of the various phenomena of hemochromatosis. Most of the opinions advanced have been based on purely theoretical grounds, and much of the discussion that has followed has been consequently almost purposeless.

6. Hoppe-Seyler, Thierfelder: Handbuch der Chem. Analyse, Ed. 8, p. 546.

7. That this figure is much less than in other reported analyses may be due to the large amount of fat tissue mixed with gland.

8. Anschütz, W.: Deutsch. Arch. f. klin. Med., 1899, **62**, 411.

9. Fitcher, T. B.: Cirrhosis with Pigmentation, Jour. Am. Med. Assn., 1901, **37**, 815; Am. Jour. Med. Sc., 1907, **133**, 78.

10. McCreery, A. H.: Canada Med. Assn. Jour., 1917, **7**, 481.

The original contention that the glycosuria was the primary factor was soon exploded as lacking any clinical or pathologic proof. The main dispute centered about the question as to whether the cirrhosis of the liver or the pigmentation of the viscera was the primary factor. In other words, did the cirrhosis of the liver result in an increase of the normal pigmentation of the viscera, or did the pigmentation of the liver and pancreas cause the cirrhosis of these organs?

TABLE 6.—IRON CONTENT OF THE VISCERA

Author and Disease	Liver, per Cent.*	Spleen, per Cent.*	Pan- creas, per Cent.*	Kidneys, per Cent.*	Retro- peritoneal Glands, per Cent.*
Stockman ¹¹ (Normal)	0.07 to 0.09 (0.182 to 0.310 gm.)†	0.144 to 0.4 (0.26 to 0.294 gm.)†			
Hopkins ¹² (Normal)	0.08 to 0.18 —	0.09 —			
Howard and Stevens..... (Hemochromatosis)	3.09	0.46	1.439	0.461	4.2
Muir and Dunn ¹³ (Hemochromatosis)	6.43 (18.0 gm.)†	0.825	2.49	0.406	11.64
Hess and Zurhelle ¹⁴ (Hemochromatosis)	7.1 (38.7 gm.)†				
Anschütz ⁸ (Hemochromatosis)	7.62 (55.7 gm.)†	5.0	Trace	14.69
Roth ¹⁵ (Case 2)..... (Hemochromatosis)	0.605	0.236	0.015	0.007 ileum 0.001 colon
Roth ¹⁵ (Pernicious anemia)	0.138 —	0.100 — —	0.132 —	0.027 ileum 0.011 colon
Stockman ¹¹ (Pernicious anemia, Case 1) (Pernicious anemia, Case 2)	0.230 (0.722 gm.)† 0.140 (0.411 gm.)†	0.086 (0.013 gm.)† 0.170			
Stockman ¹¹ (Addison's disease)	0.120 (0.396 gm.)†	0.120 (0.102 gm.)†			
Roth ¹⁵ (Cirrhotic and fatty liver)	0.025	0.040	0.013	0.007 ileum 0.006 colon
Roth ¹⁵ (Acute myeloid leukemia)	0.145	0.304	0.065	0.022 ileum 0.023 colon

* Per cent. of dried substance in every case.

† Weight of iron in grams in whole organs.

The weight of evidence seemed to favor the former supposition. Still many supported the latter theory and had to suggest the existence of some hemolytic agent which produces so much destruction of red cells as to cause an abnormal heaping up of the iron of the hemoglobin

11. Stockman, R.: Brit. Med. Jour., 1896, **1**, 1077.

12. Hopkins: Quoted by Garrod, Quart. Jour. Med., 1913-1914, **7**, 129.

13. Muir, R., and Dunn, J. S.: Jour. Path. and Bacteriol., 1914-1915, **19**, 226.

14. Hess, O., and Zurhelle, E.: Ztschr. f. klin. Med., 1905, **57**, 344.

15. Roth, O.: Deutsch. Arch. f. klin. Med., 1915, **118**, 224.

in the skin, the liver and other viscera, which in turn causes pigmentation of the skin, cirrhosis of the liver and pancreas with signs of hepatic insufficiency and glycosuria. To such a theory there are of course many objections. First, that though abnormal amounts of iron exist in the lymph glands and in many of the parenchymatous glands of the body, these do not show cirrhosis. Secondly, all writers have noted an absence of anemia or any other change in the hemoglobin content, the total number of red cells or in the size, shape or staining reaction of the cells. This we can confirm, for in our case two blood counts for weeks before the death of the patient revealed a hemoglobin of 100 per cent. by Sahli's instrument, and a red cell count of 4,280,000 and 4,440,000 per c.mm. while the leukocytes and stained red cells were normal in every respect.

Further, no observer, with the possible exception of Roth,¹⁵ has ever found clinical or postmortem evidence of this hemolytic process either in the special tests for hemolysis or in signs of regeneration in the bone marrow. It is true that in a few instances in the last few days or even weeks before death certain suggestive evidence of rapid blood destruction is available. Thus Hess and Zurhelle and Elmer have noted during life a hemoglobinuria, Letulle, Barth, Hanot, Blumer, Roth and others a mild purpura; Hindelang even a purpura hemorrhagica, and Hernandez hematuria and epistaxis. Postmortem, Quincke, Buss, Hintze and Tillmanns found one or more of the following conditions: hemorrhagic pleurisy, hemorrhagic peritonitis, hemorrhagic pericarditis, hemorrhagic pachymeningitis or cerebral hemorrhage.¹⁶ These changes are no doubt the results of a terminal infection such as occurs in many chronic diseases, and in any event have been conspicuous by their absence in the vast majority of the postmortems in hemochromatosis.

Opie¹⁷ gets around the absence of evidences of hemorrhages by the following ingenious supposition:

It seems possible that associated with some primitive alteration of the blood, there is a tendency to local hemorrhage, the hemorrhages being merely secondary manifestations of the same disease of the blood which, associated with intravascular destruction of the red corpuscles, precedes the pigment deposition.

This is of course pure speculation, and however attractive, has no foundation in fact.

Gouget,¹⁸ Roque, Chali r, Nove-Josserand, and more recently, Fiessinger and Laurent,¹⁹ have found a diminution of the globular resistance, though the latter authors noted that following on the appear-

16. Beattie, J. M.: *Jour. Path. and Bacteriol.*, 1904, **9**, 117.

17. Opie, E. L.: *Jour. Exper. Med.*, 1899, **4**, 279.

18. Gouget, M. A.: *Gaz. d.   p.*, 1910, **83**, 1238.

19. Fiessinger, N., and Laurent, L.: *Ann. de m  d.*, 1914-1915, **2**, 129.

ance of an acidosis the globular resistance became increased. Roth,¹⁵ in 1915, described a case of supposed hemochromatosis (Case 1 of his paper) with a very marked anemia, high color index, and leukopenia; the globular resistance was here also much increased. Though the necropsy revealed some pigmentation of the skin, an enlarged nodular liver, an atrophied spleen and a firm dark brown pancreas, we are inclined to doubt the validity of the diagnosis and would consider it one of cirrhosis of the liver in the course of which pernicious anemia or possibly Addison's disease developed.

We also studied the globular resistance of the cells in our case by Eppinger's modification of Chauffard and Widal's method;²⁰ hemolysis began at 0.36 and was complete at 0.30 instead of the normal figures, 0.45 and 0.34, given by Hill.²¹ In other words, three weeks before the death of our patient from acidosis the unwashed red cells showed a decreased fragility or increased resistance, as in the case of Fiessinger and Laurent. However, even if diminished globular resistance were a constant phenomenon it does not prove that the red cells have a shorter life than normal.

Gouget and Fiessinger and Laurent have repeatedly tested the blood for evidence of hemolysis, but always with negative results. Fletcher's case revealed the normal absorption bands of oxyhemoglobin and the urine was negative for hematoporphyrin. In Jeanselme's²² case the blood serum gave no hemoglobin spectroscopically.

The urobilin and urobilinogen content of the urine and feces were studied in our case and were shown to be remarkably increased two or three weeks before death. It must be borne in mind that while a similar increase occurs in pernicious anemia and other conditions in which hemolysis is marked, it is also an index of perverted liver function, and has been found by us in a variety of other conditions, as the hepatic engorgement of cardiac decompensation, acute cholecystitis and cholangitis and acute hepatitis. In other words, we believe that the extraordinary increase in the amounts of urobilin and urobilinogen in our case are indicative of a disordered liver function rather than an increased blood destruction.

As we said before, all postmortem examinations of the bone-marrow and other hematopoietic organs have failed to reveal any signs of activity which one would certainly discover in the presence of an active destruction of the circulating red cells, such as takes place in pernicious anemia. Moreover, the distribution of the iron in hemochromatosis

20. Elliot, C. A., and Kanavel, A. B.: *Surg., Gynec. and Obst.*, 1915, **21**, 26.

21. Hill, L. W.: *The Resistance of the Red Blood Cells to Hypotonic Salt Solution in the Various Anemias*, *THE ARCHIVES INT. MED.*, 1915, **16**, 809.

22. Jeanselme, M. E.: *Bull. et mém. Soc. méd. d. hôp. de Paris*, Series 3, 1897, **14**, 179.

and that of the hemolytic anemias, both the experimental and the idiopathic pernicious anemia, is quite distinct. In the former it occurs chiefly in the liver, pancreas and the retroperitoneal lymph glands, but also in certain peculiar sites as the heart muscle, the suprarenal cortex, the epithelium of the thyroid, etc. Muir and Dunn²³ found that the naked eye test for iron was almost negative in the kidneys, ileum and colon. Further, that in the kidney the microscopic iron was confined to the convoluted tubules and to some of the collecting tubules and Henle's loops. Sprunt also found in his three cases, as did we in our case, that the iron was largely confined to the tubules in the outer portion of the cortex, in the collecting tubules, especially, and in the loops of Henle occasionally. Gaskell and Vaile³ confirmed by serial sections the distribution of the pigment in the convoluted tubules of the second order and in the glomeruli. In pernicious anemia, on the other hand, the iron deposit is most marked in the liver, spleen and kidneys and can be accounted for there by a simple transference from the blood.

Muir and Dunn²³ found that in the hemolytic serum anemia of rabbits the spleen contained three times and the liver five times the amount of iron present in normal animals; that when the anemia had been completely repaired the iron content of these organs was only slightly above normal. Dubin and Pearce,²⁴ on the other hand, in hemolytic serum anemia in dogs, noted that the iron of the liver and spleen was not more than double the normal. Further, in pernicious anemia iron is not found in the retroperitoneal and parenchymatous glands. Its distribution, too, in the kidney is quite unlike that noted in hemochromatosis, being present in greater quantity and practically confined to the convoluted tubules of the first order.³ This would suggest that in pernicious anemia there is an exaggeration of the normal deposition in the various viscera from the blood, while in hemochromatosis the iron is excreted by the glomeruli and reabsorbed by the tubules of the second order; and further, there is an apparent elective affinity on the part of the cells of the liver and certain of the parenchymatous glands for the iron, whether derived from the hemoglobin or from the food.

In 1900 Meltzer²⁵ suggested that hemochromatosis might depend on a perverted iron metabolism, and that by some fault in its mechanism the organs and cells of the body retain most of the iron which reaches them on the normal round of the blood stream. If this assumption be correct, an analysis of the urine and feces would reveal any

23. Muir, R., and Dunn, J. S.: *Jour. Path. and Bacteriol.*, 1914-1915, **19**, 417; *ibid.*, 1915-1916, **20**, 41.

24. Dubin, H., and Pearce, R. M.: *Jour. Exper. Med.*, 1917, **25**, 675.

25. Meltzer, S. J.: *Med. Rec.*, New York, 1900, **57**, 43.

deviation from the normal. Parker,²⁶ in 1903, doubting the evidence of an abnormal blood destruction, suggested that the excessive deposition of iron was due to the accumulation of the products of the normal daily mortality of the red cells, which are in some way prevented from elimination by the death of the cells responsible for their removal.

In spite of Meltzer's valuable hint, it was not until 1913 that the first attempt at a metabolism study was published by Garrod and his associates.³ We, however, feel that his study is open to criticism, as in the first place the iron intake of the food was apparently estimated from tables and not directly determined. Further, he considered that the iron content of the whole blood in his case, which was 48 and 45 mg. per 100 c.c., was higher than normal, and therefore that there was iron retention in his case. Yet Fowell²⁷ had published the year before from the same hospital the results of his study of the iron content of the whole blood in thirteen normal persons and found it to range between 51 and 55 mg., or an average of 54.5 per 100 c.c. If one accepts this latter figure there was no evidence of iron retention in Garrod's case. Curiously enough, Fowell also apparently studied the iron content of Garrod's case (for the history and clinical data are identical) and found somewhat different figures, namely, 46 and 52 mg., both of which are below the normal average. Jeanselme found in the blood of his case eleven days before death an iron content of 54.2 mg., which is quite normal. At all events, Fowell's and Garrod's figures and ours show a definite decrease in the iron content of the whole blood, instead of an increased iron content, as Garrod believes. Garrod also found an absence of iron from the bile, urine and feces, which confirmed him in his suspicion that the iron was retained and not excreted in hemochromatosis.

In our study the iron was excreted entirely in the feces and not even a trace was found in the urine. The amount of iron in the feces was small, it is true, and somewhat less than the amount ingested, but there certainly was not a marked retention. At all events, both Garrod's and our case are in marked contrast to the findings in hemolytic jaundice, in which Pearce and his assistants²⁸ found the amount of iron eliminated before splenectomy was twice as great as that taken in the food. On the other hand, both in pernicious anemia of man²⁹ and in

26. Parker, G.: *Brit. Med. Jour.*, 1903, **2**, 1052.

27. Fowell, P. H. C.: *Quart. Jour. Med.*, 1912-1913, **6**, 179.

28. Goldschmidt, S., Pepper, O. H. P., and Pearce, R. M.: *Metabolism Studies Before and After Splenectomy in Congenital Hemolytic Icterus*, *THE ARCHIVES INT. MED.*, 1915, **16**, 437.

29. Pepper, O. H. P., and Austin, J. H.: *Metabolism Studies Before and After Splenectomy in a Case of Pernicious Anemia*, *THE ARCHIVES INT. MED.*, 1916, **18**, 131.

the experimental anemias of the laboratory²⁴ the elimination of iron is within normal limits, though following splenectomy in pernicious anemia as well as in hemolytic jaundice there is a marked decrease (40 per cent.) in the elimination of the iron.

The total quantity of iron in the human subject of 60 to 70 kg. body weight is, according to Sherman,³⁰ about 3.0 gm., of which more than 50 per cent. occurs in the hemoglobin molecule. Brugsch, O. David and Fowell have shown that iron exists in the blood independently of hemoglobin. Biernacki found that sometimes twice as much iron was found in the blood as was to be expected from the hemoglobin. Abderhalden concluded that hemoglobin is derived essentially from the organic iron compounds of the food, while inorganic iron, as given medicinally, acts mainly if not entirely as a stimulus.

Sherman says:

The iron of the food is absorbed from the small intestine, enters the circulation by way of the lymph and is deposited mainly in the liver, spleen and bone marrow. Its final elimination takes place mainly through the walls of the intestines.

Schmidt³¹ concluded from his experiments with normal mice that the organism possesses great powers of conserving the iron and of reutilizing it through some form of intermediary metabolism; he regards the liver as the depot of iron from the food and the spleen as the depot of iron from the tissue and red cell catabolism.

In hemochromatosis the liver alone may contain from 18 to 55 gm., or a mean of 30 gm.; in other words, one hundred times that normally found in the entire body.

As Muir and Dunn point out, there can only be one ultimate source of this excess of iron, namely, the food. The amount of iron in twenty American dietaries furnished according to Sherman is 12 to 19 mg. of iron a day, though Stockman³² gives somewhat lower figures (8 to 11 mg.). Further, the amount excreted in the feces and urine in health exactly corresponds to the amount ingested.³² Recently Groh³³ has shown that by feeding pigs with "Blutmehl" an excess of iron in the food does not lead to an accumulation of iron in the tissues, but even here the intake and output are equal.

But supposing for the sake of argument that in a disease like hemochromatosis there is a complete retention of the iron, as was believed by Garrod, it would take two years and nine months for 30 gm. to accumulate in the liver alone, even assuming that the subject was taking

30. Sherman, H. C.: *Chemistry of Food and Nutrition*, 1915, Macmillan & Co., New York.

31. Schmidt, M. B.: *Verhandl. d. deutsch. path. Gessellsch.*, 1912, **15**, 91.

32. Stockman, R.: *Jour. Physiol.*, 1895, **18**, 484; *ibid.*, 1897, **21**, 55.

33. Gröh, T.: *Biochem. Ztschr.*, 1913, **53**, 256.

in 30 mg. of iron a day, a higher figure than any diet is known to contain. The process may be a slower one, and only part of the ingested iron may be retained each day, let us say as little as was found in our case (2.5 mg. from an intake of 29.3 mg. in a five-day period), and then of course the length of time is correspondingly increased; again, assuming that in our case the moist liver weighed 1,500 gm. (which would mean 250 gm. dried), it contained 7.72 gm. of iron; for the accumulation of this amount alone (deducting 0.2 for the amount usually present) it would require over forty years. It may be objected that in our diet the iron was only one-third of what it is normally, and only one-sixth of what it was in the former supposititious case; even so, at least six years would be necessary for the retention of 7.5 gm. in the liver of our patient. Such a long period of gradual accumulation of the ingested iron is of course a possibility that cannot be denied. But we were not able to detect any retention of the iron in the blood, and no more did Fowell, or Garrod and his assistants. How, then, can we explain the evident retention, however gradual and protracted it may be? The iron from normal hemolysis may be deposited in the tissues other than those of the hematopoietic system proper, on account of some special abnormal chemical affinity of their cells for the iron, causing a greater drain on the food iron for the purposes of blood formation. This might result in a slight daily retention of the food iron with a normal or diminished iron content in the blood, as was found in our case. We, too, have been led into the realms of theory, for unfortunately we have no means of distinguishing the source of the iron, whether from hemoglobin or food, that we find in the tissues. Stockman¹¹ ventures the following suggestion:

It seems that a portion of the iron of the liver forms an integral part of the protoplasm of the cells and of their nuclei and only changes as they change while another portion is, as it were, "floating iron" and supplies the metabolic needs of the organism.

Still this again is largely theory and does not help us much.

Sprunt and his associates³⁴ have shown experimentally the liberation of iron and pigment formation in the liver during autolytic degeneration of the parenchymatous cells, independently of the hemoglobin of the blood; hence they believe these pigments may be derived from the protein constituent of the cell itself. Mackenzie Wallis³ accepts this possibility and emphasizes more particularly the nucleoprotein moiety as the source of the iron. Garrod, however, is more skeptical and believes that the source of the accumulated iron is "the normal hemolysis which must be constantly going on in the organism."

34. Sprunt, T. P., Colwell, H. S., and Hagan, H. J.: *Jour. Exper. Med.*, 1912, **16**, 607.

The total nitrogen of our patient was in perfect balance, and the nitrogen partition of the urine was normal. This proved the accuracy of our experiment, and further showed that our patient for these five days was in metabolic equilibrium.

In spite of the normal nitrogen balance there was an average daily retention of 0.1301 gm. of sulphur. We are quite at a loss to explain this, and do not deem it advisable to offer any conjectures as being unscientific. The sulphur partition of the urine was normal. We will content ourselves merely with the statement that our methods have in another experiment been proved accurate.

It is believed that normally the liver has the ability to³⁵ combine the phenols with the sulphur to form ethereal sulphates. Any disturbances of liver function, therefore, would interfere with this process and result in a disturbed ratio of free and total phenols. In our case the ratio was perfectly normal. This may mean either that this function of the liver was not affected in spite of the marked anatomic and histologic evidences of hepatic injury, or that the test is not of value. From theoretical chemical grounds the latter is the more probable explanation.

CONCLUSIONS

No fundamental conclusion can be drawn from the small amount of data available from the literature and from our study. Much more work should be done on iron metabolism, both in health and disease. We can only say that in one case studied late in the course of the disease there was evidence of a slight but definite retention of the food iron without any sign of undue destruction of red blood cells. Hemochromatosis may depend, therefore, on some injury to the liver resulting in a hepatitis, and this in turn to a disturbance of the iron metabolism, and so to a slight and prolonged retention of the iron both exogenous and endogenous.

35. Foster and Kahn, M.: *Jour. Lab. and Clin. Med.*, 1916, **2**, 25.

POLYCYTHEMIA INDUCED BY TINCTURE OF CANTHARIDES

PRELIMINARY REPORT *

SAMUEL T. LIPSITZ, M.D.
A. L. FUERTH, M.D., AND A. J. CROSS, M.D.
ST. LOUIS

In a case of tincture of cantharides poisoning which recently came under our observation,¹ a pronounced polycythemia was discovered. Inasmuch as this is a hitherto undescribed phenomenon following the introduction of cantharides into the body, and in order to eliminate any possible error in technic, we determined to study experimentally the effect of cantharides on the blood. Though there are some substances said to produce an increase in the number of red corpuscles, it is questionable whether any of them has been proved to produce an absolute and lasting polycythemia.

Lamson,² experimenting with epinephrin, was able to produce a rapid increase in the number of red corpuscles, but concluded that this was due to its specific action on the liver, causing a diminution in its size and a constriction of the hepatic capillaries. He, however, believes that when epinephrin is injected into the portal vein contraction of the liver capillaries takes place, and erythrocytes lying dormant in these vessels are thrown into the general circulation, which, with a synchronous reduction or concentration of the blood plasma, causes an increase in the number of erythrocytes per unit volume of blood. He concludes that the liver acts as a reservoir for erythrocytes. He has demonstrated that epinephrin, intravenously injected into a dog or cat causes an increase in the number of erythrocytes of 1,500,000 to 2,000,000 per c.mm. of blood in from five to ten minutes, lasting about one half hour and then gradually returning to normal. It may be deduced from his results that the effect of epinephrin in producing an increase of erythrocytes in the blood is mechanical and transitory, really limiting itself to a redistribution of the mature blood elements and manifesting itself as a relative peripheral polycythemia with

*Submitted for publication Aug. 4, 1917.

*From the Service of the Department of Internal Medicine of the St. Louis University, School of Medicine.

1. Lipsitz, S. T., and Cross, A. J.: A Case of Cantharides Poisoning with Special Reference to the Blood Picture. This issue, p. 889.

2. Lamson, P. D.: The Processes Taking Place in the Body by Which the Number of Erythrocytes Per Unit Volume of the Blood Is Increased. Proc. Nat. Acad. Sc., 1916, 2, 365.

transitory visceral anemia. It does not act through its effect on the blood-forming organs. Lamson was not able to obtain these results in similar experiments on rabbits.

It has been found that asphyxia in any form, such as is produced by carbon monoxid gas, pulmonary obstruction, passive congestion due to heart lesions, etc., causes the number of red blood cells to increase. Variations in atmospheric pressure and in the oxygen content of the blood act likewise. Lamson³ has shown that emotional stress, excitement and fright may produce transitory polycythemia. Nicotin is also said to have this effect on the blood. This is, most likely, due to its depressing action on the respiratory centers, causing partial asphyxia. Thus far, cantharides is not known to have this influence on the vasomotor mechanism, the capillaries or the liver.

Gruner⁴ states that a transitory polycythemia may rapidly appear after the incidence of hemolysis. We are not prepared to say in what way cantharides produces an increase in the number of red corpuscles in the blood. Whether it acts by affecting the vascular system of the liver or the vasomotor mechanism, or whether it acts by hemolysis and the secondary elaboration of new cells, or by the stimulation of the reservoirs of red blood cells, or whether it activates primarily the blood-forming organs, we are at present unable to say.

In our experiments we found that cantharides introduced into the stomachs of rabbits produced a definite polycythemia, not as transitory as that of epinephrin, but lasting in some instances as long as eight days. In each of twelve rabbits on which experiments were made, some increase in the number of erythrocytes per cubic millimeter was noted. In these animals as well as in the patient suffering from cantharides poisoning¹ a relative though in no way constant or characteristic increase in the number of leukocytes was also present. The hemoglobin percentage often rose and fell synchronously with the erythrocyte count. It is interesting to note that the erythremia became apparent within twenty-four to seventy-two hours after the introduction of the cantharides.

In the following experiments tincture of cantharides was administered to the animals through a soft rubber catheter inserted into the stomach.

Rabbit Experiment 1.—First day (normal erythrocyte count), 6,111,000, followed by tincture of cantharides (15 minims).

Second day (erythrocyte count), 8,740,000, followed by tincture of cantharides (30 minims). This quantity was lethal, as the rabbit died twenty-four hours later.

3. Lamson, P. D.: The Rôle of the Liver in Acute Polycythemia. Proc. Nat. Acad. Sc., 1915, **1**, 521.

4. Gruner, O. C.: Biology of Blood Cells, Macmillan Co., Toronto, 1913.

Necropsy Protocol.—The heart appeared normal; the trachea and lungs normal; the esophagus was injected and completely covered with a grayish-white eschar which could not be wiped off. The stomach showed two injected, irregular ulcers, 1 to 2 cm. in diameter. The liver showed some cloudy swelling. The kidneys were slightly enlarged and injected; the bladder was congested; urine cloudy, showing a great many white and red blood corpuscles and a few granular casts. The bone marrow appeared normal.

Rabbit Experiment 2.—Erythrocyte Count

1st day (normal).....	5,560,000	5th day.....	6,490,000
Followed by tincture cantharides (15 minims)		7th day.....	6,530,000
2d day.....	9,800,000	8th day.....	7,180,000
3d day.....	8,840,000	9th day.....	4,910,000
4th day.....	7,970,000	10th day.....	4,620,000

(See Chart 1)

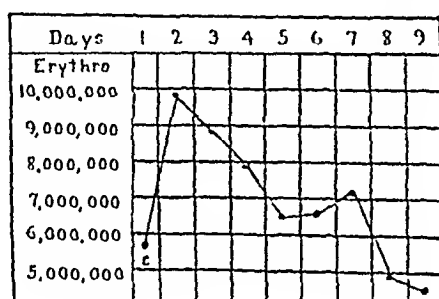


Chart 1.—Blood count and curve in Rabbit Experiment 2. In this and the following charts, C = tincture of cantharides.

Rabbit Experiment 3.—Erythrocyte Count

1st day (normal).....	6,550,000	3d day.....	8,670,000
Followed by tincture cantharides (15 minims)		6th day.....	11,260,000
2d day.....	6,310,000	7th day, rabbit developed a skin infection and had to be killed	

Rabbit Experiment 4.—Erythrocyte Count

1st day (normal).....	5,850,000	13th day.....	6,250,000
Followed by tincture cantharides (15 minims)		14th day.....	6,640,000
2d day.....	8,120,000	15th day.....	6,980,000
3d day.....	7,560,000	16th day.....	5,360,000
4th day.....	6,450,000	17th day.....	6,000,000
5th day.....	6,210,000	Followed by tincture cantharides (20 minims)	
6th day.....	6,620,000	18th day.....	7,140,000
7th day.....	6,250,000	19th day.....	7,050,000
8th day.....	6,310,000	20th day.....	7,260,000
Followed by tincture cantharides (15 minims)		21st day.....	7,000,000
9th day.....	6,620,000	22d day.....	6,600,000
10th day.....	7,230,000	23d day.....	6,720,000
11th day.....	6,950,000	24th day.....	6,990,000
12th day.....	6,730,000	25th day.....	5,620,000
		26th day.....	5,700,000

Experiment 4 shows a very consistent response to the administration of cantharides (see Chart 2).

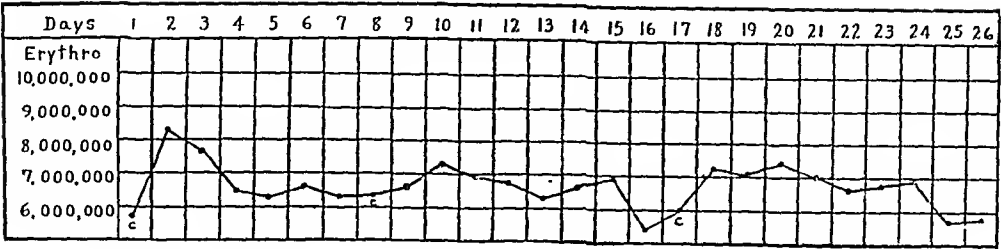


Chart 2.—Blood count and curve in Rabbit Experiment 4.

Rabbit Experiment 5.—Erythrocyte Count

1st day (normal).....	5,660,000	10th day.....	5,890,000
Followed by tincture cantharides		11th day.....	6,500,000
(20 minims)		12th day.....	7,130,000
2d day.....	6,980,000	13th day.....	7,440,000
3d day.....	6,560,000	14th day.....	5,480,000
4th day.....	7,210,000	15th day.....	5,700,000
5th day.....	8,050,000	16th day.....	7,540,000
6th day.....	6,980,000	17th day.....	7,310,000
7th day.....	5,720,000	18th day.....	7,090,000
8th day.....	5,830,000		
9th day.....	5,725,000		
Followed by tincture cantharides			
(20 minims)			

(Chart 3)

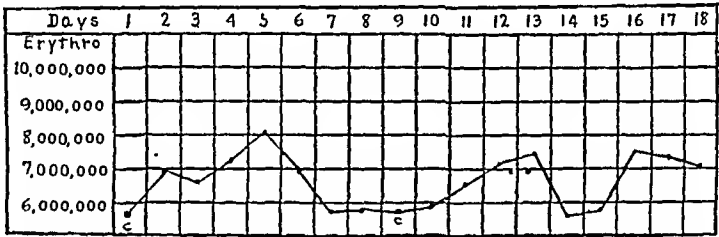


Chart 3.—Blood count and curve in Rabbit Experiment 5.

Rabbit Experiment 6.—Erythrocyte Count

1st day (normal).....	5,580,000	11th day.....	5,810,000
2d day (normal).....	5,720,000	Followed by tincture cantharides	
Followed by tincture cantharides		(20 minims)	
(20 minims)		12th day.....	6,120,000
3d day.....	5,600,000	13th day.....	6,400,000
4th day.....	6,940,000	14th day.....	6,080,000
5th day.....	6,875,000	15th day.....	5,650,000
6th day.....	5,010,000	16th day.....	5,290,000
7th day.....	7,170,000	Followed by tincture cantharides	
8th day.....	5,650,000	(20 minims)	
9th day.....	5,500,000	17th day.....	6,010,000
10th day.....	5,552,000	18th day.....	7,000,000
		19th day.....	6,800,000

Rabbit Experiment 7.—Erythrocyte Count

1st day (normal).....	6,100,000	4th day.....	8,620,000
2d day (normal).....	6,320,000	5th day.....	9,440,000
Followed by tincture cantharides		6th day.....	7,530,000
(20 minims)		7th day.....	6,700,000
3d day.....	8,010,000	8th day.....	6,370,000

Experiment 7 showed a striking rise after the cantharides administration (see Chart 4).

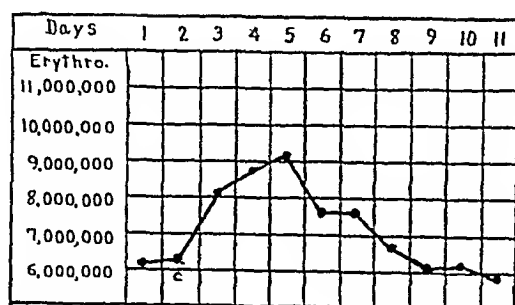


Chart 4.—Blood count and curve in Rabbit Experiment 7.

Rabbit Experiment 8.—Erythrocyte Count

1st day (normal).....	6,580,000	5th day.....	7,870,000
2d day (normal).....	6,690,000	6th day.....	7,360,000
Followed by tincture cantharides (20 minims)		7th day.....	7,160,000
3d day.....	6,650,000	8th day.....	5,980,000
4th day.....	8,280,000	9th day.....	6,120,000
		10th day.....	5,910,000

Rabbit Experiment 9.—Erythrocyte Count

1st day (normal).....	5,850,000	Followed by tincture cantharides (15 minims)	
2d day (normal).....	6,270,000	13th day.....	6,840,000
Followed by tincture cantharides (20 minims)		14th day.....	7,040,000
3d day.....	6,050,000	15th day.....	6,950,000
4th day.....	6,350,000	16th day.....	6,780,000
5th day.....	7,770,000	17th day.....	6,240,000
6th day.....	7,420,000	18th day.....	7,490,000
7th day.....	7,620,000	19th day.....	7,250,000
8th day.....	6,790,000	20th day.....	7,050,000
9th day.....	8,290,000	21st day.....	6,600,000
10th day.....	6,600,000	22d day.....	6,420,000
11th day.....	6,690,000	23d day.....	6,010,000
12th day.....	5,870,000		

(See Chart 5)

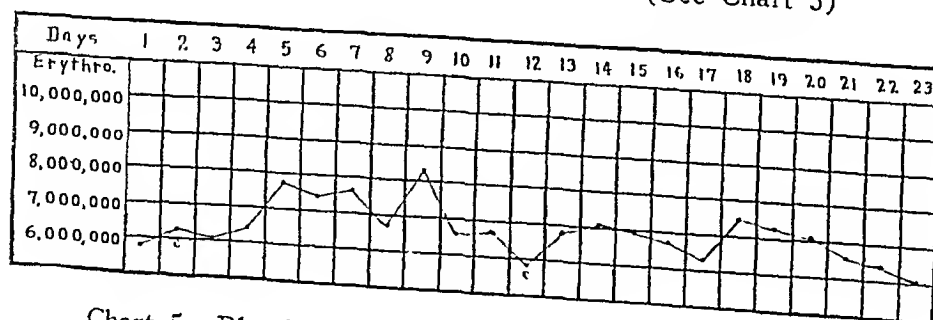


Chart 5.—Blood count and curve in Rabbit Experiment 9.

In Experiment 9 it is shown that the increase in the number of red cells following the administration of cantharides continued for a period of from seven to eight days, which is longer than that usually following the use of other substances known to have this effect. It will also be observed that after the initial rise, a secondary rise occurred in this as well as in some of our other experiments.

Rabbit Experiment 10.—Erythrocyte Count

1st day (normal).....	6,350,000	3d day.....	7,400,000
2d day (normal).....	6,710,000	4th day.....	7,540,000
Followed by tincture cantharides (20 minims)		5th day, rabbit died	

Necropsy Findings.—Right upper lobe, lobar pneumonia; acute nephritis; no other striking findings.

Rabbit Experiment 11.—Erythrocyte Count

1st day (normal).....	6,300,000	4th day.....	6,760,000
2d day (normal).....	6,880,000	5th day.....	6,520,000
Followed by tincture cantharides (15 minims)		6th day.....	7,590,000
3d day.....	7,980,000	7th day.....	5,640,000
		8th day.....	5,720,000

Rabbit Experiment 12.—Erythrocyte Count

1st day (normal).....	6,400,000	4th day.....	6,840,000
2d day (normal).....	5,850,000	5th day.....	6,910,000
Followed by tincture cantharides (15 minims)		6th day.....	6,520,000
3d day.....	7,820,000	7th day.....	5,570,000
		8th day.....	5,670,000

. CONCLUSIONS

A definite polycythemia can be experimentally produced by cantharides.

This polycythemia may be brought about with a single dose and may continue as long as eight days, when administered as in the above experiments.

It is probable that in some manner—possibly by hemolysis—it stimulates the blood-forming organs or brings about a concentration of the blood, for unlike epinephrin with its transitory action on the liver capillaries, it is slow to produce a rise in the number of red cells and slow to relinquish its effect.

OBSERVATIONS ON ACUTE MERCURIC CHLORID NEPHROSIS

WITH A REPORT OF TWO CASES *

WALTER R. CAMPBELL, M.A., M.D. (Tor.)
TORONTO, CANADA

In a recent classification of renal disease¹ the kidney lesion induced by heavy metal poisoning is classed as a nephrosis on account of the fact that there is degeneration of the tubule cells without hematuria or rise in blood pressure. Certain other factors, however, make it advisable to class these cases as "special" nephroses, thus recognizing the fact that they do not exactly parallel the types of renal disease caused either by bacteria or by their toxins. Seen in man, they form the connecting link between the ordinary clinical types of Bright's disease and the varieties produced by experimental methods. The anatomic lesion in these cases is well described by Heineke,² and consists in an acute degeneration of the tubule cells, principally of the proximal convoluted tubules, caused by the mercury in process of excretion through these cells. Very early there occur attempts at regeneration, with replacement of the degenerated epithelium by a flatter, less specialized type of epithelium and, if the injury is not too great, complete recovery ensues.

The anatomic lesion results in a functional incapacity, one expression of which is the retention in the blood of nitrogenous and other waste products. This retention is readily detected and measured by the recently developed methods of blood analysis; and these methods have therefore been widely applied to the study of kidney disease. In spite of much study it has not yet been found possible to establish exact correlation between the specific renal injury and the variety or degree of retention presented. One reason for this is doubtless to be found in the fact that clinical nephritis seldom offers an injury of one limited type. It is therefore all the more necessary to utilize for study any case in the human subject where an approximately clearcut type is represented. Such an opportunity is afforded by accidental mercury poisoning. Accordingly, mercuric chlorid nephrosis in man has, of late, received no little attention from the chemical aspect. Owing to

* Submitted for publication July 27, 1917.

* From the Department of Pathological Chemistry, University of Toronto.

1. Volhard and Fahr: *Die Brightsche Nieren-krankheit.*, Berlin, 1914.

2. Heineke, A.: *Die Veränderungen der menschlichen Niere nach Sublimatvergiftung mit besonderer Berücksichtigung der Regeneration des Epithels*, Beitr. z. path. Anat. u. z. allg. Path., 1909, **45**, 197.

the short duration of most cases, however, it is seldom possible to study on one person all the interesting features of the condition. Until we have attained a clearer idea of the relationship between the chemical and anatomic pathology of the kidney, therefore, a multiplicity of case reports is not merely unavoidable, but even desirable. This is the justification for the presentation of two new cases, one of which ended in recovery, the other in necropsy.

REPORT OF CASES

CASE 1 (Medical No. 19852).—*History*.—Miss R. S., a Hebrew, aged 19, single, V-para, was admitted to the Gynecological Department of the Toronto General Hospital Feb. 15, 1916, was transferred to the Medical Department Feb. 18, 1916, and was discharged cured, May 1, 1916.

The family history was not important.

Past History.—There were no illnesses other than measles. The patient denied venereal disease, alcoholic and drug habits. She had had five abortions (Wassermann reaction very strongly positive).

Present Illness.—On the night of February 11, she placed a mercuric chlorid tablet in the vagina to prevent conception. A marked swelling of the labia occurred and the patient experienced general malaise, with great thirst. There was no vomiting or diarrhea, melena or abdominal pain. Soreness of the mouth and gums and a metallic taste in the mouth developed and, two days later, ulcers appeared on the tongue.

On admission, in the afternoon of February 15, the temperature was 99.5, pulse 110, respirations 18.

Examination.—The patient was well nourished and did not appear acutely ill. There were several small ulcers on the tongue. The breath was foul, the vulva was markedly swollen and there were large areas of ulceration present on either labium and united anteriorly. Otherwise she was normal to physical examination. Mentally, probably an early case of dementia praecox.

Urine: Catheter specimen, acid; specific gravity 1.010. No sugar. There was much albumin and epithelium, a few leukocytes and a few red blood cells. Blood pressure, systolic 120, diastolic 85 mm. Hg; red blood corpuscles, 2,670,000; white blood corpuscles, 18,400; hemoglobin, 48 per cent. (Sahli).

Course.—The patient became worse and exhibited signs of uremia. Headache, vomiting, subnormal temperature, drowsiness and stupor developed, with a slight puffiness around the eyes and slight pretibial edema. The urine was very scanty.

February 18 venesection was performed and 500 c.c. of blood replaced by 300 c.c. 2 per cent. magnesium sulphate. Diarrhea was present at this time and much blood was found in the stools.

February 22 the patient was semicomatose, slightly irrational and had incontinence of both sphincters. After this date the patient commenced to improve. Catheter specimens of urine were acid, of low specific gravity and contained much albumin, granular casts and epithelium and a few white blood cells; no red blood cells.

February 26 the first complete twenty-four-hour specimen was obtained: 500 c.c., acid, pale, cloudy; specific gravity 1.011; albumin + + +, white blood cells, epithelium and granular casts.

February 29 the patient vomited some stomach mucosa, but continued to improve. The specific gravity of the urine rose to 1.020 and the twenty-four hour quantity to 1,300 c.c. Albumin was present but no other pathologic constituents.

April 22 albumin was not found in the urine and thereafter the urine was normal. The blood pressure varied between 110 and 120 mm. Hg systolic and

80 and 95 diastolic. The temperature varied between 97 and 100 F. and was normal as a rule. The pulse rate varied between 65 and 110 per minute. The patient was discharged as cured May 1 and was well on leaving the city May 20, 1916.

Treatment.—The patient was given much water and small quantities of milk until March 7, when she was placed on lactovegetarian diet. Hot packs were given thrice daily. Magnesium sulphate, 1 ounce, was given twice daily and compound solution of cresol douches once daily. Later Easton's syrup was used to combat the anemia.

LABORATORY RESULTS ON CASE 1

The special laboratory work on this case was confined to analyses of the blood, of which six samples were obtained. In these the nonprotein nitrogen and creatinin were determined, the former by the trichloroacetic acid method of Greenwald,³ using the Bock-Benedict⁴ distillation method, the latter by Myers'⁵ modification of the Folin method. In one specimen the sugar also was estimated, the method employed being Myers'⁶ modification of the Lewis-Benedict method.

February 18 the analysis of blood showed 232 mg. nonprotein nitrogen and 12.5 mg. creatinin per 100 c.c. The creatinin value, it may be noted, is two and one-half times as great as that which Myers and Lough⁷ believe to warrant a hopeless prognosis. From the clinical standpoint the patient became worse, but the blood on February 22 showed only 9 mg. creatinin per 100 c.c. This decrease in the creatinin preceded noticeable clinical improvement and, February 29, a further fall in the creatinin content of the blood to 5 mg. per 100 c.c. was found. By March 9 the patient was much improved. The nonprotein nitrogen was 48 mg., the creatinin 5.7 mg. per 100 c.c. of blood; blood sugar at this time was 2 mg. per c.c. The improvement of the patient continued and the blood findings parallel the clinical condition, as is shown by the following: March 29, nonprotein nitrogen 47 mg., and creatinin 3.5 mg. per 100 c.c. of blood. April 11, nonprotein nitrogen 30 mg., and creatinin 2.1 mg. per 100 c.c. These latter figures are at the upper border of the normal.

DISCUSSION OF CASE 1

The large amount of nonprotein nitrogen in the blood and its rapid fall in concentration as improvement commenced are worthy of note, but perhaps the creatinin values are, in the present case, of more particular interest.

Basing their work on the fact that of the three principal nitrogenous katabolites—uric acid, urea and creatinin—the latter is the easiest to excrete, Myers and Lough⁷ have published a series of cases to show that creatinin retention is a reliable guide to prognosis. They

3. Greenwald, I.: The Estimation of Nonprotein Nitrogen in Blood, Jour. Biol. Chem., 1915, **21**, 61.

4. Bock, J. C., and Benedict, S. R.: An Estimation of the Folin-Farmer Method for the Colorimetric Estimation of Nitrogen. Jour. Biol. Chem., 1915, **20**, 47.

5. Myers, V. C., and Fine, M. S.: The Chemical Composition of the Blood in Health and Disease, Cooperstown, N. Y., 1915.

6. Myers, V. C., and Bailey, C. V.: The Lewis and Benedict Method for the Estimation of Blood Sugar, with Some Observations in Disease, Jour. Biol. Chem., 1915, **24**, 147.

7. Myers, V. C., and Lough, W. G.: The Creatinin of the Blood in Nephritis: Its Diagnostic Value, THE ARCHIVES INT. MED., 1915, **16**, 536.

say: "Creatinin values from 2.5 to 3 mg. (per 100 c.c.) may be viewed with suspicion, figures from 3 to 5 mg. regarded as decidedly unfavorable, while over 5 mg. probably indicate an early fatal termination." While agreeing with the general contention as to the seriousness of a high and increasing creatinin content of the blood in both acute and chronic cases of kidney disease, I believe attention should be drawn to the difference between the two types which makes the generalization more particularly applicable to chronic cases. In chronic nephritis the kidney change is almost wholly degenerative in nature, that is, dead or injured cells are replaced by less specialized tissue and regeneration is at a minimum. On the other hand, while degeneration is the primary condition in acute renal disease, it is very rapidly followed by more or less complete regeneration. In chronic cases, therefore, the concentration of katabolites in the blood gradually increases with but little chance of decreasing, but, in the acute case, after the first accumulation of katabolites, due to a sudden degeneration of the tubule cells, the regenerated epithelium commences to excrete the katabolites more or less satisfactorily. In the present case nonprotein nitrogen and creatinin values were at first very high. Indeed, the latter rose far above the level at which, according to the previously quoted generalization of Myers and Lough, the prognosis should be hopeless. Nevertheless, even while the clinical condition was still considered serious, the creatinin values fell abruptly and the case progressed to a most complete recovery. The fatal import Myers and Lough attach to blood creatinin values greater than 5 mg. may be justified in cases of chronic nephritis, but the generalization is evidently not applicable to any and every case of renal lesion.

As the next case to be described terminated with all the symptoms of a uremia with nitrogen retention, it would appear likely that, in that instance, regeneration of tubule cells had not progressed with sufficient rapidity.

CASE 2 (Medical No. 20551).—*History*.—Mrs. W. P., Canadian, aged 29, married, II-para, was admitted to Ward H of the Toronto General Hospital, Feb. 26, 1917, and died March 4, 1917. The past and family history are not important.

Present Illness.—Mercuric chlorid douches were advised by some person unknown. February 21, about 9 a. m., she dissolved two tablets (17.5 grains) of mercuric chlorid in a pint of water and used the solution as a douche, retaining the fluid until it burned. In the afternoon she was seized with abdominal pains which continued three days, and vomiting lasting one day. Swelling of the face and neck, sialorrhea and mercurial stomatitis and glossitis appeared. Complete anuria commenced February 23 and lasted four days. The patient was admitted to the Toronto General Hospital during the night of February 26-27, about 132 hours after using the mercuric chlorid solution. The temperature was 98.8 F., pulse 84, and respirations 20.

Examination.—The patient was well nourished. The salivary glands were enormously enlarged. The tongue was swollen so much that she could not

close her mouth and she had difficulty in breathing. A large ulcerated area was present on the floor of the mouth, at the opening of the submaxillary salivary ducts, and several other smaller ulcers were present on the cheeks and tongue. Bloody-brown mucus and saliva dripped from the mouth in considerable quantity. The breath was horribly fetid. The patient was suffering greatly from thirst but was hardly able to swallow. The patient's thoracic organs were normal to physical examination, except for rough breathing all over the chest, probably due to pharyngeal obstruction; the liver and spleen were not palpable. There was no abdominal distress. The nervous system was normal organically, but the sensorium was slightly clouded. Genito-Urinary System: The patient was $3\frac{1}{2}$ months pregnant. Anuria had been present for four days. Urine: Catheter specimen, 1.5 c.c., acid; albumin ++; reducing substance +; granular and hyaline casts and a few white blood cells. The urine was turbid from the amount of epithelium present. Systolic blood pressure, 130 mm. Hg; red blood cells, 4,800,000; white blood cells, 19,000. The Wassermann reaction was negative.

Course.—The patient was in the hospital six days. During the first three days there was apparently a clinical improvement as measured by an increasing amount of urine and a greater interest in her surroundings and cooperation in the treatment. The condition of the tongue improved so that she was able to breathe more comfortably and the intense sialorrhea decreased. On the days following, however, the patient became more tired, dull, apathetic, resented being disturbed by treatment, refused nourishment, the mind became clouded and, on the afternoon of the fifth day, a low grade delirium commenced and delay in answering questions became very marked. The reflexes remained normal, but occasional muscular twitchings were seen and the patient aimlessly picked at one hand with the other. The inflammatory reaction around the submaxillary glands increased markedly on the fifth and sixth days. No edema of the body or fluid in the body cavities could be demonstrated. The cardiac condition remained fairly good and the lungs were normal five hours before death. The heart became more feeble, though not dilated; the lungs filled with edema, the patient became comatose and died at 5 p. m., March 4, 1917. During the illness the respiratory rate was usually 18 per minute, rising to 24 per minute in the last twelve hours. The pulse rate varied from 90 to 100 per minute. The temperature was 97 to 98 F. except on the first day. The last twenty-four hours it gradually fell to 95. The blood pressure was usually 130 systolic, and 70 diastolic, and once it was 140 systolic and 70 diastolic.

Treatment.—Treatment was based on the now well-known method advised by Lambert and Patterson,⁸ in which strenuous efforts are made to get rid of the mercury by all possible channels. As mercury is eliminated by all mucous membranes, the colon was irrigated with tap water every four hours. In the meantime the patient received by the Murphy drop method, 1 drachm potassium acetate, 3 ounces glucose in 1 pint of physiologic salt solution. To avoid gas pains the Murphy drip tube was allowed to drip into a large funnel attached to the colon tube and held at a level of 10 inches above the bed.

The patient received by mouth, imperial drink (a sweetened solution of potassium acid tartrate and lemon juice) plus 0.5 ounces lactose in each 8 ounces every two hours. Sugars were given by mouth and by rectum to reduce the protein catabolism. Nitrogenous substances were withheld, since the kidney was incapable of dealing with them. One intravenous injection of 600 c.c. of 5 per cent. glucose solution was given on the fifth day. Hot packs were given twice daily. Gastric lavage, as a means of eliminating the mercury, was of course out of the question. Saline douches were given daily and mild antiseptic mouthwashes every three hours.

8. Lambert, S. W., and Patterson, H. S.: Poisoning by Mercuric Chlorid and Its Treatment, *THE ARCHIVES INT. MED.*, 1915, **16**, 865.

Necropsy.—Performed by Dr. Robinson. Clinical Diagnosis: Bichlorid of mercury poisoning; special nephrosis; uremia; edema of lungs.

Anatomic Diagnosis.—Edema and congestion of the lungs; fatty liver with cloudy swelling; acute special nephrosis; 3½ months fetus; acute endometritis; stomatitis; gastritis; enteritis; colitis.

Kidneys: Weight, 350 gm. The right is rather soft with a number of sub-capsular petechial hemorrhages. Section: The cortex is very pale with small reddish areas scattered throughout. The cortex is 6 mm., the medulla 5 cm., a little paler than normal. Cut margins roll out. The capsule strips readily and leaves a smooth surface. The left kidney is the same as the right.

Prof. J. J. Mackenzie very kindly examined the sections and reports the following microscopic findings:

Lungs: Show a slight miliary bronchopneumonia with edema and congestion.

Gastro-Intestinal Tract: There are moderate acute inflammatory changes in the mucosa.

Kidneys: Show no glomerular change. The tubules show evidence of degeneration, granular casts plug the tubules, the epithelium is very granular and in many places has been shed. The nuclei of the tubule cells stain very well. There is considerable evidence of regeneration throughout the kidney. The small tubule cells are packed closely together, and in some cases masses of cells project out into the lumen. The lumina of the tubules is markedly dilated and there is a slight interstitial edema. The picture is that of the stage of repair.

LABORATORY RESULTS ON CASE 2

The urine was collected once daily by catheter. The patient voided spontaneously on one occasion only (fourth day). Blood was taken for analysis by venipuncture on the morning of February 27, before active treatment commenced, and immediately after death, March 4, by aspiration from the right auricle.

Methods Employed.—The reducing substance in the urine was estimated by Myers' ⁹ modification of the Lewis-Benedict picric acid method. Nitrogen was determined by Folin's micro-Kjeldahl method, ¹⁰ after precipitation of the protein by means of 25 per cent. meta phosphoric acid. Urinary chlorids were determined by a modified Volhard-Harvey method in the presence of the albumin. Creatin and creatinin were determined by Folin's method.

In the blood analysis the relative plasma volume was determined by Epstein's method, ¹¹ the nonprotein nitrogen and urea nitrogen by Folin's later methods. ¹⁰ Blood sugar was estimated by Myers' modification of the Lewis-Benedict method, ⁹ chlorids by the admirable method of McLean and Van Slyke, ¹² creatin and creatinin were determined by Folin's method as modified by Myers and Fine ⁵ and using the precautions suggested by Hunter and Campbell. ¹³ The chief results are collected in Tables 1 and 2. Besides those there shown the following points are perhaps worthy of note.

The urine was acid throughout the illness. No acetone or diacetic acid could be demonstrated. A specimen of urine previous to the poisoning was acid, specific gravity 1.025 and contained no albumin.

9. Myers, V. C.: A Method for the Determination of Small Amounts of Sugar in Urine, *Proc. Soc. Exper. Biol. and Med.*, 1915-1916, **13**, 178.

10. Folin, O., and Denis, W.: Nitrogen Determinations by Direct Nesslerization. *Jour. Biol. Chem.*, 1916, **26**, 473, et seq.

11. Epstein, A. A.: A Simplified Hematocrit and a Method for Determining Variations in Blood Volume. *Jour. Lab. and Clin. Med.*, 1916, **1**, 610.

12. McLean, F. C., and Van Slyke, D. D.: A Method for the Determination of Chlorids in Small Amounts of Body Fluids, *Jour. Biol. Chem.*, 1915, **21**, 361.

13. Hunter, A., and Campbell, W. R.: A Hitherto Neglected Factor Affecting the Determination of Minute Quantities of Creatinin, *Jour. Biol. Chem.*, 1916, **28**, 335.

TABLE 1.—ANALYSIS OF THE URINE

Date	24 Hours Volume in C.c.	Specific Gravity*	Albumin	Reducing Substance, per Cent.	Microscope		Nitrogen		Chlorids as NaCl		Creat- inint	Creatin as Creatinint
					Casts	Eplthellum	Per Cent.	Gm.	Per Cent.	Gm.		
Feb. 23-26†												
Feb. 26	1.5	+++	+	+++	+++	60	52
Feb. 27	12	1.011	+++	+	+++	+++	0.25	0.09	0.49	0.188	91	75
Feb. 28	36	1.012	+++	0.40	+++	+++	0.347	0.309	0.375	0.33	77	87
Mar. 1	88	1.014	+++	0.42	+++	+++	0.384	0.307	0.35	0.28	110	54
Mar. 2	80	1.015	+++	0.375	+++	+++	0.34	0.251	0.35	0.26	92	85
Mar. 3	74	1.014	+++	0.308	+++	+++						
Mar. 4	30	+++	+++	+++						

* Determined by weight.

† Milligrams per 100 c.c.

† Anuria.

TABLE 2.—ANALYSIS OF THE BLOOD

Date	Plasma Percentage	Nonprotein Nitrogen†	Urea Nitro- gen†	Blood Sugar, per Cent.		Chlorids per Cent. in Plasma	Creatinint		Creatin as Creatinint	
				Whole Blood	Plasma		Whole Blood	Plasma	Whole Blood	Plasma
February 27.....	69	170	109	0.2	0.2	0.663	16.1	7.75	23.9	20.85
March 7.....	69	319	200	0.46	0.521	0.521	21.3	23.7	48.6	40.8

† Milligrams per 100 c.c.

No mercury could be detected in 50 c.c. of saliva. Mercury was found in the first washings of the colon, but could not be found in the intestinal contents at necropsy. Sufficient urine was not available for daily tests, but a combined specimen for March 1, 2 and 3 showed the presence of large amounts of mercury. The Vogel and Lee¹⁴ test was used.

Blood was never present macroscopically in the colon washings. Its presence was demonstrable by the benzidin test, however.

The carbon dioxid tension in the alveolar air was 30 mm. Hg by Marriott's method.

DISCUSSION OF CASE 2

The Urine.—The specific gravity of the urine was low throughout, though it rose somewhat as the case progressed, reaching its maximum of 1.015 on March 2. In acute simple nephrosis, while salt excretion is markedly diminished, the nitrogen percentage is generally high (even as much as 3 per cent.).¹ In the present case, however, both salt excretion and nitrogen excretion were low, both in percentage and absolute amount. This is the usual picture in the acute special nephroses such as mercuric chlorid poisoning. Its explanation is not difficult to imagine. There appears to be pretty conclusive evidence that not only the nitrogenous substances, but also the salts¹⁵ are excreted by the tubule cells, and in particular, by those of the proximal convoluted tubule. In mercuric chlorid nephrosis all, or nearly all, of these cells have been poisoned by the mercury in the process of excretion, and consequently the cells are not in a condition to excrete either salts or nitrogen.

The constant presence of albumin, hyaline and granular casts, and epithelium hardly calls for comment. No red blood cells or blood casts were seen and the benzidin test was negative after boiling the urine, thus indicating the probable absence of glomerular change (Volhard and Fahr¹).

The reducing substance present in the urine is a curious feature in the case. Benedict's qualitative reagent was reduced quite strongly, and, as estimated by Myers' modification of the picric acid method,⁹ each specimen contained the equivalent of 0.3 to 0.4 per cent. of glucose. The reducing substance, however, would not ferment with pure yeast, nor would it yield an osazone or rotate polarized light either when cleared by filtration or mercuric acetate. Barfoed's test, Reigler's test, Nylander's test, and the orcin and phlorglucin tests for pentoses

14. Vogel, K. M., and Lee, O. I.: Detection of Mercury in the Excretions, Jour Am. Med. Assn., 1914, **62**, 532.

15. Basler, A.: Ueber Ausscheidung und Resorption in der Niere. Arch. f. d. ges. Physiol. (Pflüger's), 1906, **112**, 203; Biberfeld, J.: Beiträge zur Lehre von der Diurese, **10**, *ibid.*, 1904, **105**, 308; Brown, C. P.: On the Distribution of Potassium in Renal Cells. Trans. Canad. Inst., 1912, p. 389; Roehl, W.: Ueber Kalkablagerung und -Ausscheidung in der Niere. Beitr. z. path. Anat. u. z. allg. Path., Supp. 7, 1905, p. 456; Waschetko, N.: Ueber die Ausscheidung des Natriumferrocyanats durch die Niere beim Hunde, Ztschr. f. Biol., 1909, **53**, 128.

and glycuronic acid were negative. When defecated with solid lead acetate neither filtrate nor precipitate appeared to contain a reducing substance. On the question whether or not this substance was being excreted before the poisoning we have no conclusive evidence. The patient's previous medical attendant thinks not.

The Blood.—The estimation of the relative plasma volume was carried out on blood oxalated by the addition of 20 per cent. potassium oxalate in the proportion of one drop to 3 c.c. of blood. This involves a certain degree of dilution, so that the plasma volumes found are a little too high. The error involved was determined in several instances, by direct comparison with herudinized samples of the same blood, to be about 5 per cent. The plasma volume of normal blood, oxalated in the way described, was never found to exceed 62 per cent.¹⁶ The present case with its observed plasma volume of 69 per cent. exhibited a definite hydremia.

The values obtained for the nonprotein nitrogen and urea nitrogen are very high, but have been exceeded by cases of mercury poisoning reported by other observers—notably Myers and Fine.¹⁷ Underhill¹⁸ has reported a case of recovery after a urea nitrogen level of 240 mg. per 100 c.c.

As the patient was receiving no nitrogenous food, the increase in urea and nonprotein nitrogen is due wholly to metabolic destruction of body protein. If one is to judge from the temperature, there was no important toxic breakdown of body protein, and therefore the protein was being used solely for the energy needs of the body. It was with the idea of sparing, as far as possible, such consumption of body protein that a carbohydrate diet was administered. It was hoped by this means to hold the concentration of nonprotein nitrogenous substances in the blood at a low level until sufficient regeneration of the proximal convoluted tubule cells had taken place to permit of the kidney excreting them.

On the first analysis there was a moderate hyperglycemia of 2 mg. per c.c. of blood or plasma, as was the case also in the previous patient. On the second occasion the blood sugar content of the whole blood and plasma had risen to more than four times and more than five times, respectively, the normal values. Though the case is not an isolated

16. Corrected Value, 57 Per Cent. In this connection compare Keith, Rowntree and Geraghty: A Method for the Determination of Plasma and Blood Volume, *THE ARCHIVES INT. MED.*, 1915, **16**, 547, who find the same average value, using solid sodium oxalate as an anticoagulant.

17. Myers, V. C., and Fine, M. S.: The Nonprotein Nitrogenous Compounds of the Blood in Nephritis with Special Reference to Creatinin and Uric Acid, *Jour. Biol. Chem.*, 1915, **20**, 361.

18. Underhill, A. J.: Blood Urea in Renal Conditions, *New York Med. Jour.*, 1915, **102**, 662.

instance, it is not common for the plasma sugar to be so much greater than the whole blood sugar. While hyperglycemia, as has been shown by Myers and Bailey,⁸ is frequently enough encountered in kidney disease, it does not appear to be an invariable accompaniment of the nephrosis caused by heavy metal poisoning. In fact, in the latter condition hypoglycemia seems to be as frequent as hyperglycemia. Frank,¹⁹ for instance, refers to the frequency of glycosuria without hyperglycemia in experimental heavy metal nephrosis. Cohen and Bernhard,²⁰ in their case of mercury poisoning, found hypoglycemia with 1.5 per cent. of sugar in the urine. On the other hand, Lewis and Rivers²¹ found a moderate hyperglycemia, but account for its presence by the therapeutic measures adopted. This consideration does not arise in either of the present cases, which, incidentally, are the only cases on our records showing a hyperglycemia with uncomplicated renal disease.

It is obvious from the patient's general condition that estimations of Ambard's coefficients were impossible. A certain amount of interest, however, attaches to the determinations of the chlorids of the plasma and the urine. In the ordinary case of simple nephrosis the patient is unable to excrete chlorids and often develops an enormous anasarca. In the special nephrosis, which includes mercury poisoning, the excretion of sodium chlorid is small, but demonstrable edema is, as a rule, absent. Woods²² and Lewis and Rivers²¹ have reported cases of mercuric chlorid poisoning with very low blood and plasma chlorids. Heineke and Meyerstein²³ found low concentrations of chlorids in experimental chromate nephrosis. The initial analysis in the present case showed a normal concentration of chlorids in the plasma, but at the exitus the plasma chlorid value was markedly below the normal threshold value of 5.62 gm. per liter. McLean²⁴ has reported a case of uremia showing a similar course. The explanation offered by McLean for his case, namely, that the low plasma chlorids resulted from the developing acidosis, is a possible one in this case, since a definite acidosis was demonstrated by low alveolar carbon dioxid tension. Other possible explanations appear to be inadequate. In view of the

19. Frank, E.: Ueber experimentelle und klinische Glykosurien renalen Ursprungs, *Arch. f. exper. Path. u. Pharmakol.*, 1913, **72**, 387.

20. Cohen and Bernhard: A Case of Mercurial Poisoning with Recovery, *Jour. Am. Med. Assn.*, 1916, **66**, 1019.

21. Lewis, D. S., and Rivers, T. M.: Chemical Studies on a Case of Bichlorid Poisoning, *Bull. Johns Hopkins Hosp.*, 1916, **27**, 193.

22. Woods, A. C.: Studies of the Nitrogen Partition in the Blood and Spinal Fluid, *THE ARCHIVES INT. MED.*, 1915, **16**, 577.

23. Heineke, A., and Meyerstein, W.: Experimentelle Untersuchungen über den Hydrops bei Nierenkrankheiten, *Deutsch. Arch. f. klin. Med.*, 1907, **90**, 101.

24. McLean, F. C.: The Chlorids of the Plasma in Uremia, *Proc. Soc. Exper. Biol. and Med.*, 1915-1916, **13**, 166.

constancy of the relative plasma volume, the suggestion of Georgopoulos,²⁵ that hydremic plethora accounts for the low plasma chlorids, cannot be accepted. It seems equally unlikely that the low plasma chlorids are the effect of a developing pneumonia,²⁶ for the bronchopneumonia in this case was slight and very recent. Considering the high initial and low final chlorid content of the plasma, I cannot agree with Lewis and Rivers²¹ that the low chlorid excretion was due to the concentration of plasma chlorids being below the threshold value.

The data on the creatinin of the blood deserve perhaps some comment. Hitherto attention has been paid to the concentration of this substance in the whole blood only, but it is selfevident that, on the side of the blood, the factor immediately affecting the excretion of any substance is its concentration in the plasma. This may or may not be the same as the concentration in the whole blood. As a matter of fact, a long series of analyses made in this laboratory²⁷ have demonstrated that the creatinin, as determined by the method of Folin, is practically always at a lower concentration in the plasma than in the whole blood. Out of 125 instances, normal and pathologic, examined, only three (all pathologic and all showing at least 18 mg. per 100 c.c.) have proved to be exceptions to this rule. One of these exceptions is offered by the case now under consideration. At the first examination the whole blood creatinin and plasma creatinin are each about eight times the normal values and the whole blood contains twice as much as the plasma. At death, however, while the whole blood creatinin had increased to 21.3 mg., the plasma creatinin was even greater. It would therefore appear that, as the blood creatinin rises, the substance accumulates for a time, not only in the plasma, but also in the corpuscles; but that there is a limit to the amount which the corpuscles can take up. When that limit is passed the usual relation becomes reversed and the plasma creatinin is higher than that of the whole blood. In all three instances of this phenomenon that have come to my observation the plasma creatinin was over 20 mg. per 100 c.c. Whether this represents a real limiting concentration of general significance remains to be determined. In any case it is obvious that the figures for the plasma reveal much more strikingly than do those for the whole blood the rapidly increasing resistance of the kidney to the

25. Georgopoulos: Experimentelle Beiträge zur Frage der Nieren Wassersucht, *Ztschr. f. klin. Med.*, 1906, **60**, 411.

26. McLean, F. C.: The Numerical Laws Governing the Rate of Excretion of Urea and Chlorids in Man, II, *Jour. Exper. Med.*, 1915, **22**, 366.

27. Hunter, A., and Campbell, W. R.: The Distribution of Creatinin and Creatin Between the Corpuscles and Plasma of the Blood, *Proc. Am. Soc. Biol. Chem.*, December, 1916; *Jour. Biol. Chem.*, 1917, **18**, 29; and further unpublished data.

passage of creatinin.²⁸ So far as I am aware, these are the first data to be published on the plasma creatinin in renal cases.

I wish to thank Dr. Ross for permission to study and report these cases, Professor Mackenzie and Dr. Robinson for permission to use their notes, and my chief, Professor Hunter, for his assistance and advice.

28. For a further discussion of the relationship between the whole-blood creatinin and plasma creatinin see a forthcoming paper by Hunter and Campbell (*Jour. Biol. Chem.*, November, 1917). It will there be shown, in agreement with the views of Wilson and Plass (*Wilson, D. W., and Plass, E. D.: Creatin and Creatinin in Whole Blood and Plasma, Jour. Biol. Chem.*, 1917, **29**, 413) that the method of Folin, though giving correct values for plasma, exaggerates the creatinin content of whole blood, and that with the technic of Myers, as employed in the work here reported, this effect is even more pronounced. The contrast between the plasma creatinin and the whole blood creatinin of Case 2 was, therefore, in reality more remarkable than the figures would make it appear. The limiting value at which the plasma creatinin exceeds that of the corpuscles is for the same reason probably considerably lower than 20 mg. In fact, since the foregoing was written, one case, at least, has been encountered in which a blood containing, according to the original Folin technic, 3.76 mg. yielded a plasma with 3.85 mg. of creatinin.

STUDIES ON ACIDOSIS

THE IMMEDIATE CAUSE OF DEATH, AND REMARKS ON THE ACIDOSIS OF
NEPHRITIS *

JAMES L. WHITNEY, M.D.
SAN FRANCISCO

The immediate cause of death is a subject of great practical as well as scientific interest. The essential similarity in the condition of most patients within a few hours of death is well recognized, yet the underlying causes of collapse, and even such physiologic sequences as the state of the circulation, the respiratory apparatus, etc., are either unknown or but vaguely understood. Why does an organism which has succeeded in carrying a load of disabilities for perhaps many years break down and cease to functionate at one particular time rather than another? On the answer to this question must depend any rational treatment.

We must first inquire just what is meant by death. The body as a whole may be said to have died when both respiration and heart beat have permanently ceased. But we know that the heart possesses a wonderful intrinsic power of contraction, and that long after so-called death a heart which has stopped beating may be made to resume its action either by artificial respiration or even by perfusion of the excised organ with suitable fluids. This is doubtless to be explained on the assumption that the heart itself is not dead, but that its action is inhibited for the time being by soluble substances, the asphyxial waste products of its own metabolism and function. The respiratory center, however, has no such power of resistance. It is known that the nervous centers are extremely sensitive to asphyxia, and that none of them will survive lack of appropriate blood supply for more than about eight minutes. After this time resumption of function is impossible even though circulation returns. Evidently, then, the death of the respiratory center is the essential element in the death of the body as a whole. In accordance with this it is well known that the respiration fails in the great majority of cases many minutes before the heart stops beating. In certain cases, of course, circulatory conditions may be the primary cause of death with failure of the respiration following immediately from lack of blood supply to the center. Thus, trauma to the heart, ventricular fibrillation, and perhaps other abnormalities of the heart-beat mechanism, may bring death as well as peripheral causes

* Submitted for publication July 12, 1917.

* From the Department of Medicine and the George Williams Hooper Foundation for Medical Research, University of California.

such as large hemorrhage, embolism, intracranial pressure higher than systolic pressure, etc.

In considering causes of death of the respiratory center we will put to one side primary failure in blood supply, also failure of oxygenation (asphyxia, drowning, gas poisoning) and trauma to the center itself. We shall still be left with the great majority of cases of death, and in these it seems evident that the failure of the respiration is due to soluble poisons acting on the center itself. Many drugs, of which morphin is an example, have a powerful depressing effect. Others, such as acids of any kind, have a primary stimulating effect, but in larger doses cause paralysis and death. It has been rather vaguely assumed that in morbid states certain soluble poisons accumulate which act in this way on the respiratory center, but little is known as to the nature of such poisons. Even in the case of the nitrogenous retention of nephritis we do not know which are the toxic bodies. Whipple¹ has shown that the cause of death in intestinal obstruction and probably in pancreatitis, peritonitis and other conditions is a toxic proteose, but it is not clear whether it is this proteose itself which poisons the respiratory center or some one of the products of the vigorous catabolism which the proteose causes in all the tissues of the body. Very little is known as to the nature of the poisons of infectious diseases and next to nothing about the supposed toxins liberated by malignant growths. Vaughan's work on split products of proteins and Jobling's on non-specific intoxications give promise of further development of the highest importance.

It is evident that an enormous amount of research will be needed to clear up the problems suggested in this field, and the following paper is only a preliminary report on one phase of work being done by several investigators in these laboratories. The subject of protein catabolism in terminal conditions has already been attacked by Whipple, Cooke¹ and others by study of the incoagulable nitrogen in the blood. The cases of the present series have yielded some interesting data in regard to nitrogenous metabolism, but anything like a complete discussion must be reserved for the future, and the matter will be barely mentioned here.

In applying the convenient Van Slyke² method for estimating acidosis it was noticed that in a wide variety of cases the test ran

1. Whipple, Rodenbaugh and Kilgore: Intestinal Obstruction. V. Proteose Intoxication. *Jour. Exper. Med.*, 1916, **23**, 125. Cooke, Rodenbaugh and Whipple: Intestinal Obstruction. VI. A Study of Noncoagulable Nitrogen of the Blood. *Ibid.*, 1916, **23**, 717.

2. Van Slyke, D. D.: *Proc. Soc. Biol. and Exper. Med.*, 1915, **12**, No. 7. (Since the present paper was written Van Slyke's method has been described in full, with a series of papers on its application and on various aspects of acidosis, written by Van Slyke and associates (*Jour. Biol. Chem.*, 1917, **30**, 289, ff). For theoretical discussion of the whole matter the reader is referred to this series.)

parallel with that intangible but clinically fairly definite entity known as "condition"—the sicker the patient the more likely he was (with important exceptions) to show acidosis. It was soon found that the majority of patients at the moment of death show a very marked acidosis.

THEORY OF ACIDOSIS

The fundamental theories of acidosis have been so often presented in recent writings³ that it is hardly necessary in this place to cover the ground anew. The most essential elements in the question are (a) the mixture of salts in the blood (and body as a whole), of which the most important are the phosphates and the carbonates and dissolved carbon dioxid, which mixture shows (b) a very high resistance to change of reaction, its so-called "buffer-value"; (c) the action of the carbon dioxid as the easily variable factor in the complex, at the same time activating and being itself regulated by the respiratory center; (d) the strict proportion always found between the various radicals in this complex, and hence the propriety of measuring the total carbonates in the blood as a substitute for the alveolar carbon dioxid; (e) the inverse relationship between alveolar carbon dioxid, hence total carbonates, and the degree of acidosis.

In the production of acidosis two factors are of importance: (a) the rate of appearance of acid ions in the body, and (b) their rate of elimination. The latter is again dependent on (a) factors of kidney sufficiency, (b) other methods of elimination as by bowel, sweat glands, etc., and probably (c) certain factors having to do with the affinity of the tissues (including the blood itself) for the various radicals.

As to this last point, it may safely be predicted that the research of the next few years will reveal facts of the greatest importance. There is much reason to believe that a great many of the phenomena of elimination and retention, hitherto explained on the basis of selective action of the kidneys, lowered efficiency, etc., will be found to depend on the giving up or holding back of these substances by the tissues and the blood. In other words, that a kidney eliminates within the limits of its efficiency those substances which are available in the blood for elimination, and fails to eliminate others which are bound to protein or other substances in tissues and blood by affinities which cannot easily be broken.

SHOCK

This conception is of great importance in relation to acidosis, and especially in relation to conditions of so-called shock, including in this

3. For a rather elementary review of the principles of acidosis and for a bibliography reference may be made to an article by me in the *Boston Med. and Surg. Jour.*, 1917, **177**, 225.

category most cases of impending death from any cause. To make this assumption of identity between shock and other terminal states may perhaps seem like begging a very important question. I know of no definition of shock, however, which does not include the ordinary features of death from most nonsurgical causes such as infection, nephritis, tumor, etc., for example, rise in pulse, fall in blood pressure, failure of fluid metabolism, hippocratic facies, dyspnea followed by gasping respiration, etc. In default of proof to the contrary it would seem a safe working hypothesis that the same physiologic processes may be going on in all such cases.

While it is impossible in this place to enter on the very controversial questions as to the cause of shock, a brief reference to the salient points seems desirable. The fundamental facts of the behavior of the circulatory apparatus in this condition have been established by Yandell Henderson⁴ and amply confirmed by others, though Henderson's assumption of acapnia, the result of overventilation, as the usual primary cause of these phenomena, has received little support. His proof is definite, however, that in the first stage of shock there is a loss of venous tone with accumulation of a "lake" of blood in the great venous plexuses and the consequent failure of venous return to the heart. For this reason the heart output is diminished to a point where the tissues begin to suffer from asphyxia, and eventually blood pressure falls, which up to this time has been maintained by a vigorous overaction of the arterial vasomotors, compensating for decreased cardiac output. At about this time a crisis occurs, and it is found that efforts to restore blood pressure by increasing the volume of blood (infusion, transfusion) will be only temporarily successful, since the fluid no sooner enters the vessels than it streams out into the tissues and the volume in circulation falls again within a few minutes to the point of insufficiency.

The first stage of shock, that of venous stasis alone, may or may not be of common occurrence in other than surgical conditions, but there is every reason to believe that the crisis referred to above does occur in a wide variety of conditions, and that this last stage where there is a violent imbibition of fluid by the tissues with depletion of blood volume represents the terminal event in the majority of cases of death. The reason for this failure of the fluid to remain in the vessels is naturally of the first importance. Henderson believes it to be the result of asphyxia of the tissues, and assigns as intermediate in the process the acid products known to be formed where oxygenation is

4. Henderson, Y.: Acapnia and Shock. VII. The Failure of the Circulation. *Am. Jour. Physiol.*, 1910, **27**, 152.

insufficient. In this he follows Martin Fischer⁵ in his well-known theory that the tissues of the body show the same tendency that is observed in other colloids to imbibed fluid when subjected to the influence of dilute acid. This again is a highly controversial question, but the results reported in the present paper are certainly of interest in this connection. For if the blood almost without exception shows acidosis in conditions which we believe to be indistinguishable from this final stage of shock, this must not only represent an acid condition of the tissues, but, since the acid comes from the tissues and is not formed in the blood itself, represents actually a higher acidosis in the tissues than is found in the blood. Fischer, and, following him, Henderson would have us believe that this tissue acidosis is primarily the cause of the demoralization of the circulation in terminal states. It is perhaps worth pointing out, however, that it is by no means proved that the one condition is dependent on the other, but that both may be the result of other factors of unknown nature.

To return to the causation of acidosis in general: It is evident that there may be at least two classes of cases showing this condition: first, those of overproduction of acid, as in diabetes, starvation, cyclic vomiting, the acidosis of violent exercise, mountain-sickness, etc., and second, those of retention of acids with or without overproduction, whether due to failure of kidney function or to abnormal affinities of the tissues. It will of course often be difficult to determine whether certain cases belong in one class or the other, and in cases where both factors operate, to decide which is of greater importance.

EFFECT OF ACIDOSIS ON THE RESPIRATORY CENTER

The effect on the respiratory center of increase of acid radicals in the blood has been already referred to as being primarily stimulation, eventually paralysis. It is to be remembered that any ordinary increase in acid radicals in the blood is almost entirely compensated for by loss of carbon dioxide, so that the existence of a certain degree of so-called acidosis need imply but little increase in hydrogen-ion concentration. When the acidosis becomes more marked, however, this compensatory mechanism is bound to break down, and we shall at this time see the physiologic effect on the respiratory center of the rising hydrogen-ion concentration. It makes little difference whether this finally increased acidity is due to carbonic or to other acids. Since the work of Haldane, Barcroft, Hasselbalch and others it has been believed that the respiratory stimulus depends on hydrogen-ion concentration alone, irrespective of the nature of the acid radicals involved. Hooker⁶ has recently

5. Fischer, Martin: *Edema and Nephritis*, New York, 1915.

6. Hooker, Willson, and Connett: *Am. Jour. Physiol.*, 1917, **43**, 351.

arrived at results by perfusion experiments which lead him to believe that carbon dioxid has a stronger action on the respiratory center than other acids. The question is a difficult one, but at any rate the difference, if such exists, is quantitative, not one of kind.

In observing the effect on animals of increased hydrogen-ion concentration (whether by introducing a fatal amount of fixed acid or by increasing the carbon dioxid in the blood) one is struck by the similarity in the manner of death to that observed in clinical cases. As death approaches the breathing becomes more rapid and deeper until dyspnea is violent; then rather suddenly follows a break into a gasping, irregular respiration, less and less effective in keeping down the rapidly mounting carbon dioxid of the blood, and eventually respiratory paralysis.

THE DEGREE OF ACIDOSIS NECESSARY TO CAUSE DEATH

In order to test the degree of acidosis necessary to cause death, as expressed in terms of blood carbonates, we have introduced dilute hydrochloric acid into the stomachs of three rabbits causing death in from one half to one and one half hours. Beforehand the Van Slyke readings were 47, 51 and 52, respectively. Blood taken at time of death showed 12, 14 and 16. These figures are of the same order as many of those taken from patients, showing that in certain of these at least the acidosis alone was a sufficient cause of death.

REPORTS OF CLINICAL CASES

In the series here reported the cases were entirely unselected. The interns were asked to procure a specimen of oxalated blood by heart puncture in every case of death from any cause, most of the specimens being obtained within ten minutes after that event. Many specimens were also taken from patients in bad condition and from others not in bad condition where an eventual fatal outcome was possible. At first only the Van Slyke test was applied, but in the later specimens of the series the incoagulable nitrogen and blood urea were estimated as well.⁷

Table 1 gives in abbreviated form the results of this study, showing the presence of a more or less marked terminal acidosis in a wide variety of conditions. For the sake of emphasis only the Van Slyke readings at time of death are given, arranged in order of the degree of acidosis found. According to Van Slyke a reading of 50 is the lower limit of normal, and anything below this point may be taken to indicate acidosis.

7. For great assistance in these latter determinations I have to thank Dr. J. V. Cooke.

TABLE 1.—BLOOD CARBONATES MEASURED AT TIME OF DEATH

Series No.‡	Hospital No.	Diagnosis	Blood Carbonates
1	10437	*Pernicious anemia, bronchopneumonia.....	5.0
42	12946	*Enlarged prostate, postoperative pneumonia.....	8.0
2	11426	†Pernicious anemia, probable pneumonia.....	9.0
46	12978	*Chronic nephritis, acute pleurisy.....	12.5
33	11411	*Myocarditis, bronchopneumonia	14.5
3	11114	*Pernicious anemia, bronchopneumonia.....	16.5
4	11491	*Pernicious anemia, miliary tuberculosis.....	16.5
27	13112	†Lung abscess, empyema.....	18.0
41	10894	*Pyonephrosis, bronchopneumonia	19.0
7	11549	*Leukemia, noma	19.0
5	11004	*Pernicious anemia, bronchopneumonia.....	19.0
49	12283	*Chronic nephritis, bronchopneumonia.....	21.0
31	11057	*Otitis meningitis, bronchopneumonia.....	22.0
61	12462	*Acute yellow atrophy, bronchopneumonia.....	22.0
17	10819	*Postoperative bronchopneumonia	22.0
18	12218	†Bronchopneumonia	23.0
62	10890	†Postoperative peritonitis, ileus.....	27.5
11	11884	*Active endocarditis	28.0
63	12339	*Postoperative peritonitis, bronchopneumonia.....	28.0
21	12623	†Lobar pneumonia	28.0
67	12782	*Carcinoma liver, endocarditis.....	29.5
22	12871	†Lobar pneumonia	29.5
64	13019	*Postoperative peritonitis, ileus.....	29.5
48	12432	†Chronic nephritis	31.0
60	12743	*Myxedema, bronchopneumonia	31.5
63	11118	*Sarcomatosis	33.0
69	11143	*Carcinoma stomach, bronchopneumonia.....	33.5
32	10952	*Miliary tuberculosis	34.0
34	12696	*Myocarditis, bronchopneumonia	34.0
70	10910	†Carcinoma stomach, bronchopneumonia.....	35.5
71	11224	*Carcinoma esophagus, bronchopneumonia.....	36.0
20	11370	*Postoperative bronchopneumonia	36.5
12	12919	*Pick's disease	39.0
35	10945	*Cardiac disease, bronchopneumonia.....	38.5
36	11218	*Pernicious anemia, acute bronchitis.....	39.0
36	12083	*Myocarditis, acute bronchitis.....	41.5
37	11546	*Chronic valvular disease, sudden death.....	48.0
75	11032	*Fatal hemoptysis (tuberculosis).....	54.5
65	12300	*Gastric tetany	61.5
66	12479	*Gastric tetany	78.5

* Necropsy diagnosis. † Clinical diagnosis; necropsy refused.
 time of death. ‡ These are the series numbers in Tables 2 to 8.

† Specimen taken at

From Table 1 the main thesis of the present paper is evident at a glance. Out of forty cases of death from different causes, all except three showed a more or less marked acidosis at time of death. In many of these the acidosis was of such degree that this alone could have led to respiratory paralysis, and this factor may therefore be assumed to have been the immediate cause of death. In other cases the acidosis, though present, seems hardly of a fatal degree, and we must suspect that other toxic factors have cooperated in the fatal result.

Beside the three patients showing readings above 50, one other (Case 37) was just below the line and had no greater acidosis at death than he had previously shown. This patient, an old cardiac case, died suddenly while standing by his bed, probably of ventricular fibrillation, for it was observed that he continued to breathe for some time after his heart had stopped beating. One patient (Case 75) bled to death suddenly in a large hemoptysis. Evidently in these two cases there was no intoxication of the respiratory center. Cases 65 and 66 were both cases of gastric tetany and confirm in a striking way the assertion that this condition shows a so-called alkalosis (Table 7). Both cases show also a very high incoagulable nitrogen, being similar in this respect to cases of intestinal obstruction. These interesting observations must pass without further comment here, since the intoxication of gastric stasis is being studied further and will be considered in later reports from these laboratories.

Having thus established the fact of a terminal acidosis in the majority of cases of death, we may turn to a more detailed examination of the data from these and other cases for interesting suggestions as to the origin and significance of this acidosis. For this purpose I have divided the cases into groups on the basis of diagnosis, adding to the fatal cases of Table 1 certain others of a similar nature which were not fatal or which were not studied in the final stage.

ANEMIA

Table 2 shows a number of cases of severe anemia of which the first seven were fatal. The severity of the terminal acidosis in these cases is striking, six of the seven having readings below 20. In each of these there was a severe infection. That severe anemia without infection does not necessarily show acidosis is proved by the earlier readings of Cases 1, 2 and 6, in one case quite normal, in the other two nearly so. It is also shown by Cases 8, 9 and 10. Evidently, if anemia is not a prime cause of acidosis, the latter must be the result of something else, in these cases doubtless the infection. The extreme degree of the acidosis might be interpreted as indicating that this was the only toxic factor in these cases of anemia, since readings for blood

ACIDOSIS

1917

carbonates are of the same magnitude as those cited above for rabbits killed by acid alone. It may be remarked, however, that Case 6 evidently had some obscure intoxication of a different nature from every other case in this series. Her blood a week before death showed a normal Van Slyke reading and normal incoagulable nitrogen, and yet she was comatose and evidently moribund. The fact that she lingered so long in this condition showed, however, that she needed the *coup de*

TABLE 2.—CASES OF SEVERE ANEMIA

No.	Hospital No.	Sex	Age	Diagnosis	Date	Blood Carbonates	Incoagulable Nitrogen	Remarks
1	10437	♂	60	*Pernicious anemia; slight chronic nephritis; bronchopneumonia	5/ 9/16 5/13/16†	43.0 5.0	Hemoglobin 5
2	11426	♀	52	†Pernicious anemia; probable bronchopneumonia	5/24/16 5/28/16†	40.0 9.0	Hemoglobin 8
3	11114	♀	46	*Pernicious anemia; bronchopneumonia	4/ 1/16 4/ 3/16 4/ 5/16†	26.0 11.5 16.5	Hemoglobin 10 Moribund; given transfusion
4	11491	♀	54	*Pernicious anemia; miliary tuberculosis	6/ 3/16 6/ 6/16†	41.5 16.5	Hemoglobin 10
5	11004	♂	73	*Pernicious anemia; arteriosclerosis; stricture of urethra; cystitis; pyelitis; bronchopneumonia	3/16/16 3/16/16†	24.0 19.0	5 hours antemortem, hemoglobin 8
6	11213	♀	56	*Pernicious anemia; arteriosclerosis; acute bronchitis; acute cystitis	4/18/16 5/ 9/16 6/ 3/16 8/28/16 9/30/16 11/ 4/16 11/10/16†	55.5 51.0 55.0 52.0 57.5 53.5 39.0 47.6 37.1 30.7	Hemoglobin 15 Hemoglobin 10 Hemoglobin 10 Hemoglobin 10 Hemoglobin 5; comatose; looks moribund
7	11549	♀	41	*Lymphatic leukemia; noma	6/27/16†	19.0		
8	10912	♀	57	Pernicious anemia	3/ 3/16 4/ 8/16	57.5 60.5	Hemoglobin 15
9	11201	♀	48	Pernicious anemia	4/17/16	62.0	Hemoglobin 20
10	11159	♀	39	Carcinoma of bonemarrow?	4/ 8/16	56.5	Hemoglobin 15; died 2 months later

* Necropsy diagnosis.

† Clinical diagnosis; necropsy refused.

‡ Specimen taken at time of death.

grâce of acidosis, which was eventually furnished without doubt by the acute bronchitis.

RELATION OF INFECTION TO ACIDOSIS

The influence of infection in calling forth acidosis deserves special attention. A direct relationship is strongly suggested by the fact that the great majority of patients dying with acidosis showed infection of some kind, and by the fact that a number of patients who were near death from one cause or another failed to show acidosis until the final hours when the terminal infection may be presumed to have first

exerted its influence. The commonness of terminal infection has long been recognized in patients dying with chronic disease. It would seem almost fair to say that certain abnormalities such as kidney incompetence, circulatory failure, malignant disease, etc., cannot unaided furnish the toxin which is necessary to paralyze the respiratory center; this poison must be furnished in the majority of cases by an infection for which of course the underlying chronic process has prepared a

TABLE 3.—CASES OF ENDOCARDITIS AND GENERAL SEPSIS

No.	Hospital No.	Sex	Age	Diagnosis	Date	Blood Oarbo-nates	Ineoag- ulable Nitro- gen	Remarks
11	11884	♂	25	*Acute and chronic endocarditis; mitral stenosis; aortic insufficiency; relative tricuspid insufficiency; pulmonary infarct	10/20/16 10/24/16 10/26/16 10/30/16 10/31/16	45.0 43.0 36.5 28.0	87.4 133.4 107.8 107.3 139.1	Toxic; jaundiced
12	12919	♂	34	*Chronic endocarditis; aortic, mitral and tricuspid insufficiency; chronic peritonitis and pleurisy; acute pericarditis (Pick's disease); myocarditis; bronchopneumonia	6/ 2/16 12/27/16 12/28/16 12/28/16	69.0 47.0 45.0 38.0 60.7 81.2 92.3	Not very sick Reenters after cerebral embolism 11 hours antemortem
13	11436	♂	48	Chronic endocarditis with acute recurrence; mitral and tricuspid insufficiency	12/27/16 12/29/16 1/ 9/17 1/12/17 1/16/17 1/23/17 1/31/17	35.5 41.0 42.0 33.0 34.0 40.0 32.0	55.1 34.6 84.0 76.5 78.4 58.8 60.2	Jaundiced; very sick Afterward recovered from acute process and largely from decompensation
14	12364	♂	28	Acute endocarditis; aortic and mitral insufficiency; acute nephritis	10/ 5/16 10/13/16 10/25/16 11/ 8/16 11/10/16 11/16/16 41.0 49.0 30.5 35.5 41.5	73.4 59.8 71.4 79.8 74.5 87.3	Died elsewhere a month later
15	12368	♂	17	*Acute endocarditis; pericarditis; pleurisy; peritonitis (Pick's disease); mitral and tricuspid insufficiency	10/ 6/16 10/13/16 10/25/16 1/31/17	61.5 52.0 62.5	38.3 41.6 38.8 47.6	Died March, 1917
16	13050	♀	25	*Streptococcus septicemia (postpartum); pelvic and femoral thrombophlebitis; peritonitis; erysipelas; acute nephritis	1/16/17 1/23/17	45.0 39.0	55.0 60.6	Died Feb. 28, 1917

* Necropsy diagnosis.

† Specimen taken at time of death.

favorable soil. From the data here furnished it would seem justifiable to conclude that the particular poison which the infection calls forth and by which the respiratory center is paralyzed is an excess of acid. In this series only five of the thirty-two cases coming to necropsy failed to show fairly marked evidence of infection. One (Case 68, Table 8) clinically recognized as Hebra's pityriasis rubra, gave the microscopic picture of sarcomatous infiltration of skin and lymphatic structures. There was no evidence of infection either by cultures or

by the appearance of the parenchymatous organs. The other four were the cases referred to above as showing no acidosis (one of ventricular fibrillation, one of hemoptysis, two of tetany). In other words, there was infection present in every case which showed acidosis except one.

On the other hand, it appears that acidosis may be wholly lacking in certain cases of quite severe infection. Tables 3 and 4 include those cases in the series in which the primary condition was infectious, eliminating those in which the infection was concomitant or terminal. Of the seven patients with endocarditis and septicemia (Table 3) all except one show low carbonate and high nitrogen figures. This one (Case 15) had the clinical features of a cardiac decompensation and the infection was low grade. The acidosis in Case 12 was terminal and the estimation made on a previous entry was high. This case also should be considered as a cardiac case (a typical Pick syndrome) and the infection was low grade. In Cases 14 and 16 the patients had an acute nephritis as part of their sepsis, and renal insufficiency has to be considered (these cases are included also in Table 6). Cases 11 and 13, however, are particularly interesting as showing a rather marked constant acidosis and a high incoagulable nitrogen, and in neither case was there evidence of more than renal congestion. In Case 11 necropsy showed no nephritis, in spite of an incoagulable nitrogen of 133 mg. a week before death. This must be interpreted as representing a rapid tissue catabolism due to the morbid process, and perhaps the acidosis has the same significance. The infections of Table 4 give various findings. In the more serious and fatal ones the patients show acidosis, though several who seemed quite sick give normal readings. For example, Case 30, a typhoid patient, gave normal readings. Also Case 18, one of bronchopneumonia in a demented old man, showed no acidosis in the earlier stages. More striking still was Case 23, a young man at the height of the intoxication of a lobar pneumonia. Both carbonates and incoagulable nitrogen were normal. The probable explanation of lack of acidosis in these cases is that the extra production of acid ions caused by disease can be taken care of by the powers of elimination of the normal body, but rapidly causes a fatal acidosis when the latter are seriously impaired by nephritis, marked intoxication of the kidney, failure of water elimination, etc. This may explain why pneumonia, with its low mortality for young and previously healthy persons, is so deadly for the aged and for sufferers from chronic disease, perhaps most of all from nephritis.

For the most part this terminal acidosis due to infection is of quick development, usually being followed by death within a few days, sometimes within a few hours, illustrating that the checks against acidosis

are extremely efficient in most conditions, and also that once these checks are overcome the accumulation is rapid and fatal.

Cases of localized chronic sepsis, as in empyema, certain postoperative peritoneal infections, etc., show as a rule little or no acidosis. Case 26 showed acidosis at the first appearance of a postoperative lung condition, but as this developed into pulmonary abscess and empyema the normal figure was resumed. Patient 28, who had a large collection of pus, was not very sick and shows normal readings. This makes an

TABLE 4.—CASES OF PNEUMONIA AND OTHER INFECTIONS

No.	Hospital No.	Sex	Age	Diagnosis	Date	Blood Carbo-nates	Incoag- ulable Nitro- gen	Remarks
17	10819	♀	59	*Bronchopneumonia, post-operative (carcinoma of cervix)	3/10/16†	22.0		
18	12218	♂	74	†Bronchopneumonia; arterio-sclerosis; dementia	9/23/16 9/28/16 9/30/16 10/ 8/16†	52.5 58.0 53.5 23.0	45.7 62.4 63.0	
19	11384	♀	54	Postoperative pneumonia	5/27/16 5/28/16	43.5 44.5	Recovery
20	11370	♂	63	*Bronchopneumonia; post-operative (operation for duodenal ulcer, June 7); arteriosclerosis; myocarditis	6/ 8/16 6/ 8/16†	37.5 36.5	3 hours antemortem
21	12623	♀	37	†Lobar pneumonia; delirium tremens	11/11/16 11/12/16†	44.0 28.0	51.5 84.0	
22	12871	♀	60	†Lobar pneumonia; chronic alcoholism	12/18/16 12/10/16†	46.0 29.5	72.8 74.7	
23	12582	♂	22	Lobar pneumonia	10/ 7/16	55.5	42.0	5th day; temperature 41 C.; very sick; recovery
24	11164	♂	35	Bronchopneumonia; asthma	4/10/16	42.0	Temp. 39 C.; recovery
25	11352	♂	36	Tuberculosis of lungs; pneumothorax	5/11/16	48.0	Temp. 40 C.; discharged, not improved
26	12262	♀	42	Postoperative pneumonia; probably embolic (operation for salpingitis September 25); abscess of lung; empyema (operation for empyema October 20)	9/26/16 9/27/16 9/28/16 9/30/16 10/25/16	45.0 51.0 59.5 62.5 56.5	79.3 62.3 58.4 44.1	Died October 30
27	13112	♀	23	†Abscess of lung; streptococcus empyema	1/23/17 1/25/17†	39.0 18.0	46.6 69.0	Just before operation, very septic
28	13134	♂	57	Empyema (operation January 25)	1/25/17 1/29/17 1/31/17	61.5 61.5	74.2 48.2 30.8	Just before operation, not very sick; recovery prompt
29	10966	♀	8	Scarlatina	3/ 3/16	29.5		
30	12669	♂	8	Typhoid fever	12/ 3/16	51.5	33.6	Temp. 40 C.; recovery
31	11057	♀	8	*Streptococcus meningitis; otitis media; bronchopneumonia	3/25/16 4/ 1/16†	39.5 22.0	Almost normal for child
32	10952	♂	9 mo.	*Miliary tuberculosis; meningitis	3/ 9/16 3/11/16 3/11/16†	57.5 42.6 34.0	High reading for a baby ¼ hour antemortem

* Necropsy diagnosis.

† Clinical diagnosis; necropsy refused.

‡ Specimen taken at time of death.

interesting contrast with the other empyema case, Case 27, in which the process was fulminating and marked acidosis was present. These chronic pus cases with their high readings may be compared with cases to be referred to later (Table 7) of probable proteose intoxication. They suggest a strong probability that there is absorption of autolytic products, presumably proteoses, going on in any case which involves a considerable production of pus, thus giving a picture similar to that described by Whipple in intestinal obstruction.

TABLE 5.—CASES OF CARDIAC INSUFFICIENCY

No.	Hospital No.	Sex	Age	Diagnosis	Date	Blood Carbo-nates	Incoag- ulable Nitro- gen	Remarks
33	11411	♂	70	*Arteriosclerosis; myocar- ditis; passive congestion; bronchopneumonia	5/20/16 5/24/16 5/25/16 5/28/16†	47.0 51.5 47.0 14.5		
34	12696	♂	68	*Arteriosclerosis; myocar- ditis; mitral and relative tricuspid insufficiency; slight chronic nephritis; enlarged prostate; cystitis; bronchopneumonia	11/28/16 12/ 8/16 12/13/16 12/13/16†	45.0 41.0 34.0	50.4 56.9 98.8 101.2	5 hours antemortem
35	10945	♂	26	*Myocarditis; mitral and rel- ative tricuspid insuffi- ciency; erysipelas; pulmo- nary infarct; broncho- pneumonia	3/ 9/16 3/25/16 4/14/16 4/18/16†	52.5 47.0 56.5 38.5	During erysipelas
36	12083	♂	77	*Arteriosclerosis; myocar- ditis; relative tricuspid insufficiency; slight chronic nephritis; acute bronchitis and pleurisy	10/27/16 10/30/16 11/ 8/16 11/10/16 11/11/16 11/13/16 11/16/16 11/17/16†	43.5 56.5 44.0 45.0 52.5 52.5 41.5	24.3 58.8 56.2 69.1 71.9 103.1 90.5	
37	11546	♂	60	*Aortic stenosis and insuffi- ciency and mitral insuffi- ciency; adhesive pericar- ditis; arteriosclerosis	6/14/16 8/28/16 9/23/16 10/ 6/16 10/ 7/16†	61.5 48.0 51.0 48.0	35.0 41.1 53.9	Death sudden, heart stopping before respira- tion
38	10956	♂	49	Aortic insufficiency; some- what decompensated	3/10/16	60.0		
39	10968	♂	53	Aortic insufficiency; some- what decompensated	3/11/16	55.5		
40	11174	♂	52	Emphysema; tricuspid in- sufficiency; anasarca; cya- nosis	4/14/16 4/21/16 10/27/16 1/16/17	69.0 76.0 76.0 68.0	42.9 42.0	

* Necropsy diagnosis.

† Specimen taken at time of death.

CARDIAC CASES

Comparison of the cardiac and the kidney cases in this series is interesting. While the latter all show a marked acidosis in their later stages, those of fairly pure cardiac disease show little, and then usually as a purely terminal event (Table 5). In fact, some of the readings

are notably high, as in Case 40. Apparently pretty severe circulatory difficulty alone neither causes the production of acid nor the failure of its elimination. The fact that a certain degree of acidosis is present at death even in these cases would imply that this contributes at least to the fatal result, but emphasizes the importance of other factors. It may be assumed, for example, that with a badly impaired circulation to the respiratory center less of an alteration in the blood itself might be fatal than if the supply were abundant. Further, we have some data to be published later showing that certain cardiac cases have abnormally high alveolar carbon dioxide and blood carbonates, particularly where there is marked cyanosis. We are inclined to attribute this to depression of the respiratory center, so that the latter tolerates an increase in the hydrogen-ion concentration of the blood (what might be called a carbonic acidosis), though the possibility of a simple concentration in the blood of alkalis and salts in general has not yet been eliminated.

THE ACIDOSIS OF NEPHRITIS

Table 6 shows cases of nephritis or other kidney disease causing insufficiency. Of these the first two were primarily general sepsis, though an acute nephritis also existed. They have already been referred to above. Cases 41 and 42 showed marked renal insufficiency, but had also a strong element of sepsis. Case 43 was of rather mild acute nephritis. The next six cases (44 to 49) were of the active (parenchymatous) stage of nephritis, with more or less toxemia and interference with renal function. Cases 50 to 55 were of the less active and generally more advanced type, usually called interstitial. They were well enough compensated to show good function. The last four cases, though primarily of nephritis, showed cardiac decompensation to a degree that rather overshadowed the former condition.

It has been known since the paper of Lewis, Barcroft,⁸ etc., that certain cases of nephritis may show a considerable degree of acidosis, but the factors governing this matter have not been recognized.

The cases in the present series are perhaps too few to warrant positive statements, yet they strongly suggest that certain generalizations may be made. First, it is hard to escape the conviction that the presence of acidosis is distinctly a function and result of renal insufficiency. Considering only those cases which are relatively uncomplicated by infection or cardiac failure, it will be seen that the acidosis and other evidence of renal insufficiency were remarkably parallel. Those cases having a two-hour phenolsulphonephthalein output below 30 show acidosis, while those above 30 mostly do not. In the same way the incoagulable nitrogen and the acidosis run parallel, though here there

8. Lewis, Ryffel, Wolf, Cotton and Barcroft: *Heart*, 1913, 5, 45.

TABLE 6.—CASES OF NEPHRITIS AND RENAL INSUFFICIENCY

No.	Hos- pital No.	Sex	Age	Diagnosis	Date	Blood Carbo- nates	Inco- agu- lable Nitro- gen	Blood Urea Nitro- gen	Blood Pres- sure	Phthal- cin, 2 Hrs.	Remarks
14	12364	♂	28	Active endocarditis; aortic and mitral insufficiency; acute nephritis	10/ 5/16 10/13/16 10/25/16 11/ 8/16 11/10/16 11/16/16 41.0 49.0 30.5 35.5 41.5	73.4 59.3 71.4 79.8 74.5 87.3	22.5 27.2 34.7 46.2 50.4 44.2	115 140 145 165	25 25 14	Died elsewhere a month later
16	12050	♀	25	*Streptococcus septicemia (postpartum); pelvic and femoral thrombophlebitis; peritonitis; erysipelas; acute nephritis	1/16/17 1/23/17 2/ 8/17	45.0 39.0	55.0 60.6	26.6 23.5	165	31 38 ...	Died Feb. 28
41	10894	♀	7	*Adenomata of kidneys with pyonephrosis; relative mitral and tricuspid insufficiency; bronchopneumonia	2/28/16 3/ 1/16 3/ 3/16	24.7 30.5 19.0 178.6	15	Died Mar. 4
42	12746	♂	76	*Enlarged prostate (operation Dec. 6); chronic pyelonephritis; chronic nephritis; bronchopneumonia	12/ 1/16 12/14/16 8.0 292.0	176 ...	36 ...	
43	13324	♂	35	Acute nephritis; chronic tonsillitis	2/21/16 2/23/16 2/27/16 55.5 57.8 31.9	170 150 ...	15 38 ...	
44	11410	♂	46	Chronic nephritis; edema; retinitis	5/19/16 5/20/16 5/22/16 5/25/16 6/ 7/16 6/20/16 50.0 39.0	12.8 20.0 10.6	210	20 ... 24 40 ...	
45	12224	♂	38	Chronic nephritis; retinitis	9/16/16 9/23/16 9/25/16	53.0 57.5 56.5	50.0 66.0 69.1	24.1 31.8 28.4	210	30	
46	12978	♂	45	*Old tuberculosis right kidney with stones; chronic nephritis, left kidney; retinitis; acute pleurisy	1/ 3/17 1/21/17 1/26/17	41.0 12.5	95.7 264.1	47.6 115.9	282 150 ...	16	
47	12492	♀	34	Chronic nephritis; retinitis	10/26/16 11/ 8/16	35.5 37.5	120.4 123.7	65.0 81.2	200 ...	15 ...	
48	12432	♀	48	Chronic nephritis; retinitis	10/15/16 10/20/16 10/26/16 10/27/16 10/28/16 68.0 58.5 52.5 31.2 59.7 150.3 213.7 240.3 24.1 58.3 124.0 71.1	180 225	33	
49	12283	♂	43	*Chronic nephritis, advanced, with acute exacerbation; retinitis; myocarditis; bronchopneumonia	9/24/16 9/25/16 9/27/16	41.0 34.5 21.0	158.6 170.8 231.0	96.6 106.8 84.0	220	20	
50	11187	♀	58	Chronic nephritis; retinitis	5/ 9/16 5/25/16	60.4 52.5	250 ...	50 ...	
51	13313	♀	41	Chronic nephritis; retinitis	3/ 3/17	58.5	190	45	Postpartum case. Delivery Feb. 17
52	12223	♀	56	Chronic nephritis; retinitis	9/25/16	54.5	40.1	20.7	230	75	
53	11212	♂	59	*Chronic nephritis; arteriosclerosis; bulbar paralysis	4/ 2/16 4/17/16	65.0 58.5	11.2 ...	230 ...	60 ...	Died April, 1917

* Necropsy diagnosis.

† Specimen taken at time of death.

TABLE 6.—CASES OF NEPHRITIS AND RENAL INSUFFICIENCY—(Continued)

No.	Hos- pital No.	Sex	Age	Diagnosis	Date	Blood Carbo- nates	Inco- agu- lable Nitro- gen	Blood Urea Nitro- gen	Blood Pres- sure	Phthal- cin, 2 Hrs.	Remarks
54	12518	♂	51	Syphilis; arteriosclerosis; chronic nephritis; retinitis	10/27/16	56.5	48.5	19.6	200	50	
55	12551	♂	25	Chronic nephritis; retinitis	11/ 4/16	51.5	60.7	26.4	220	42	
56	11186	♀	59	Carcinoma cervix; chronic nephritis; hypertrophy and dilatation of heart	4/24/16	67.1	225	25	
57	11111	♂	65	Chronic nephritis; myocar- ditis; arteriosclerosis; dementia	4/ 1/16	42.3	170	35	Died elsewhere 2 weeks later
58	18030	♂	52	Chronic nephritis; retinitis; hypertrophy and dilata- tion of heart	1/12/17	50.0	67.6	38.6	210	25	
59	11954	♂	49	Chronic nephritis; retinitis; myocardial insufficiency	8/28/16	53.0	48.5	21.8	200	32	Died elsewhere 2 mos. later

are interesting exceptions. In Case 44 the patient showed a normal urea nitrogen in the blood, in spite of a rather low phenolsulphone-phthalein output, but was very miserable; had marked edema, headaches, anemia, vomiting; he showed acidosis. Case 48, on the other hand, did not at first appear so sick, but the rapidly mounting nitrogen retention was followed by a speedy death. Her phenolsulphone-phthalein output was only measured once, at 33, and later may have been lower. It is interesting that her Van Slyke readings were normal up to the day before death, with an incoagulable nitrogen of 214. From this case it would appear that kidney insufficiency alone does not necessarily cause acidosis — suggesting that there must be an abnormal production of acid as well as a failure of elimination.

The same thing is shown pretty clearly by four experiments on dogs summarized in Table 9. In the first three dogs the kidneys were removed under ether after withdrawal of a normal specimen of blood. The first dog was in poor condition before the operation (suspected distemper) and survived less than twenty-four hours, having developed a moderate acidosis. (It will be seen that the normal Van Slyke readings in dogs are lower than in human beings, and also that they seem to be more variable.) The other two showed no acidosis, but of course a very high nitrogen. The fourth dog was given an acute nephritis by three doses of corrosive sublimate; he lived nine days, during which his blood carbonates, though variable, could not be said to indicate acidosis until the last day, and then not a very considerable degree. Necropsy in the last three dogs showed no evidence of infection, and it seems clear that there could have been no very rapid formation of

acid through the metabolism of these dogs, since their power of elimination of this substance must have been small, being restricted to the ability of the bowel and sweat glands (?) to eliminate acid.

From the data of the human and the experimental cases combined the following generalizations would seem to be justified:

Renal insufficiency is a very important factor in the causation of acidosis, by failure of elimination.

TABLE 7.—CASES OF MISCELLANEOUS INTOXICATIONS

No.	Hos- pital No.	Sex	Age	Diagnosis	Date	Blood Carbo- nates	Incong- ulable Nitro- gen	Remarks
60	12743	♀	49	*Myxedema; bronehopneu- monia	12/ 3/16 12/ 4/16†	51.5 31.5	52.3	
61	12462	♀	24	*Acute yellow atrophy of liver; bronchopneumonia	10/19/16†	22.0	56.2	
62	10890	♂	19	†Renal calculus (operation March 2); peritonitis (op- eration March 7); ileus (enterostomy March 8)	3/ 6/16 3/ 7/16 3/ 8/16 3/ 9/16 3/10/16 3/11/16 3/13/16 3/14/16†	47.5 58.0 42.0 40.5 31.0 22.0 27.5 117.0	Before operation Before operation Looks better Slightly better Considerably worse Stupor
63	12339	♂	50	*Carcinoma of stomach; gastrectomy November 8; wound infection and fis- tula; peritonitis; arterio- sclerosis; bronehopneu- monia	11/10/16 11/13/16 11/16/16 11/20/16†	57.5 47.0 28.0	53.8 83.7 60.2 109.2	
64	13019	♀	30	*Salpingitis; cystic ovary; gallstones (operation Jan- uary 10); general perito- nitis; paralytic ileus	1/13/17†	29.5	88.7	
65	12300	♀	62	*Carcinoma of gallbladder; adhesion about duodenum, causing stenosis and gas- tric stasis; coma	10/14/16†	61.5	234.7	
66	12479	♂	60	*Carcinoma pylorus with stenosis; tetany	10/26/16 10/27/16†	129 (1) 78.5	129.7 161.0	

* Necropsy diagnosis.

† Clinleal diagnosis; necropsy refused.

‡ Specimen taken at time of death.

To this must usually be added an increased production of acid, since a kidney which is markedly insufficient by other tests (Case 48) may still keep the acid threshold normal.

This increased formation of acid may apparently be a result of the toxemia which is the primary cause of an active parenchymatous nephritis (Case 44).

It is often called forth by an intercurrent infection, and of course greatly increases the danger from the latter.

CERTAIN INTOXICATIONS WITHOUT ACIDOSIS

Brief reference must now be made to certain toxic conditions which are not accompanied by acidosis, but which may lead to death or almost to that point (Tables 7 and 8).

The interesting intoxication of gastric stasis (Cases 65 and 66) has already been noticed, as also that in Case 6 of pernicious anemia.

Through the courtesy of Dr. Whipple I have had the opportunity to measure the blood carbonates on several of his experimental dogs which were moribund from the effects of proteose intoxication following intestinal obstruction. The resulting figures were normal or rather high, showing that proteose intoxication either has no effect on the acid metabolism, or may even work against the development of acidosis. In the human series there are two cases of ileus, peritonitis, etc. (Cases 62 and 63 of Table 7). Both of these show absence of acidosis at a time when the incoagulable nitrogen indicates a very seri-

TABLE 8.—CASES OF MALIGNANT TUMOR

No.	Hos- pital No.	Sex	Age	Diagnosis	Date	Blood Carbo- nates	Incoag- ulable Nitro- gen	Remarks
67	12782	♂	60	*Carcinoma of bile duct with metastases; infarction spleen and kidney; arteriosclerosis; slight acute endocarditis	12/ 8/16 1/ 9/17 1/31/17 2/ 9/17 57.5 29.5	35.9 46.6 46.7 81.2	9 hours antemortem
68	11118	♂	34	*Sarcomatosis of skin and lymph nodes	4/10/16 4/14/16	33.5 33.0		
69	11143	♀	65	*Carcinoma of stomach and peritoneum; chronic nephritis (not marked); bronchopneumonia	4/24/16 4/26/16 4/26/16	51.5 44.0 33.5	Comatose, moribund 2 hours antemortem
70	10910	♂	68	†Carcinoma of stomach; arteriosclerosis; slight chronic nephritis; bronchopneumonia	3/ 2/16 3/10/16 4/17/16 5/28/16 6/ 5/16 6/ 6/16	54.5 49.0 57.5 54.5 50.0 35.5	Exploratory operation March 28 Slow failure until death
71	11224	♂	62	*Carcinoma of esophagus; bronchopneumonia	4/19/16	36.0		
72	12322	♂	61	Lymphosarcomatosis	10/20/16 10/25/16	55.5	54.1 75.6	Died on train a week later
73	12389	♂	28	Hodgkin's disease	10/20/16	54.5	62.9	During fever period
74	12358	♀	45	Sarcoma of chest wall.....	10/ 6/16 10/30/16	59.5 57.5	36.4 35.9	Large sloughing mass Died March 8, 1917

* Necropsy diagnosis.

† Clinical diagnosis; necropsy refused.

‡ Specimen taken at time of death.

ous proteose intoxication. Both, however, had some acidosis at death, probably referable to the infection present.

The suggestion has already been made above that high carbonate readings in chronic pus cases may indicate the same sort of intoxication.

By Dr. Whipple's courtesy again, I have estimated the carbonates in four dogs dying of the peculiar intoxication which results from the Eck fistula. In these cases also the readings were normal or high.

There may be a severe intoxication in cases of malignant tumor in which acidosis is absent or only appears in the last hours of life. Case 69 of Table 8 illustrates this. This woman was comatose and

evidently dying, yet showed no acidosis two days before death. Case 70 showed the same thing. Nitrogen estimations were not made in these two cases, but other data in our possession as well as published reports from others prove that such cases may show a high incoagulable nitrogen when the toxemia is severe.

THERAPEUSIS

I feel obliged to add a few words on the subject of therapeusis, chiefly to warn against indiscriminate use of alkalis in cases such as those here described, at least in the present state of our knowledge. The neutralization of the acid ions is not the only thing to be considered; the salts thus formed must be eliminated, otherwise they may

TABLE 9.—EXPERIMENTAL RENAL INSUFFICIENCY IN DOGS

	Date	Incoagulable Nitrogen	Blood Carbonates	Remarks
Dog 1	5/31/16	37.4	40.5	Normal blood, followed by nephrectomy
	6/ 1/16	188.0	29.0	Found dead
Dog 2	6/ 6/16	37.8	33.5	Normal blood, followed by nephrectomy
	6/ 7/16	112.0	39.5	
	6/ 8/16	196.0	31.5	
	6/ 9/16	327.0	36.5	Found dead
Dog 3	6/12/16	30.8	32.5	Normal blood, followed by nephrectomy
	6/13/16	119.0	—	
	6/14/16	262.0	47.0	Found dead
Dog 4	6/23/16	36.0	46.0	Normal. 11 mg. HgCl ₂ per K. injected in lumbar muscles
	6/29/16	33.5	32.5	
	6/30/16	78.0	34.5	
	7/ 1/16	75.0	35.5	
	7/ 2/16	70.0	—	Second injection of same dose
	7/ 3/16	191.0	39.5	
	7/ 4/16	—	38.5	Third injection of same dose
	7/ 5/16	151.0	43.0	
	7/ 6/16	197.0	39.5	
	7/ 7/16	369.0	24.0	Died as blood was being taken

Note.—The first three dogs starved during the experiment. Dog 4 had one dog biscuit daily.

well accumulate to an abnormal and possibly highly dangerous concentration in blood and tissues. If elimination is so poor as to allow accumulation of acid there is every reason to suppose that salts may also be retained. Obviously, the indication will be to promote diuresis by giving as large quantities of fluid as is considered safe, either by mouth, under the skin or perhaps best by Murphy drip. Glucose may be added both as an available food and because of its powerful diuretic action.⁹

Warning should be given against indiscriminate use of morphin in cases of acidosis on account of its depressing action on the respiratory center.

9. It has been shown by Woodyatt that glucose acts as a diuretic only if hyperglycemia is produced. This might be done deliberately by the intravenous use of rather strong glucose solutions, but could probably hardly be accomplished through rectal administration. Woodyatt, R. T.: Harvey Lectures, 1917.

Finally, fresh air is indicated—a gentle breeze across the face which will blow away the expiration and prevent the rebreathing of carbon dioxid which ordinarily occurs, as Crowder¹⁰ has shown, and which in acidosis may prove to be the little extra strain which the respiratory center cannot survive.

SUMMARY

The great majority of human cases studied showed a more or less marked acidosis at time of death.

In many of these the acidosis was of such degree that it may well have been the cause of death.

In others a lesser degree of acidosis was found which, combined with other toxic factors, may have caused death.

These results bear out to a certain degree the theories of Henderson and Fischer as to shock.

Infection seems to have a very marked influence in causing acidosis. All but one case in this series showing acidosis had evidence of severe infection. The cases which did not show acidosis did not have infection. A patient may, however, have marked infection with intoxication and show no acidosis provided his powers of elimination are active.

Two cases of death due to circulatory failure showed no acidosis.

Two cases of pyloric stenosis with tetany showed an alkalosis as well as a very high incoagulable nitrogen, indicating a severe intoxication.

Certain obscure toxemias are mentioned which are not necessarily accompanied by acidosis; for example, those of intestinal obstruction, Eck fistula, malignant tumors and pernicious anemia.

In all fatal cases, where the incoagulable nitrogen was estimated there was an increase at time of death, often very great, this indicating doubtless a marked tissue destruction.

Certain heart cases, though severe, may show lack of acidosis or an actual increase in blood carbonates, but they, too, are likely to show a certain degree of acidosis immediately before death.

As a result of the study of a series of cases of nephritis it appears that two factors are necessary to produce acidosis: failure of the power of elimination and an increase in the production of acid in the body. Cases with two-hour phenolsulphonephthalein output over 30 per cent. show acidosis only if there is a severe toxemia, while those below 30 per cent. show acidosis as a rule.

As causes of increased acid production in nephritis, the toxemia of the active parenchymatous form is itself operative; infection is an even more powerful factor.

10. Crowder, T. R.: On the Reinspiration of Expired Air, *THE ARCHIVES INT. MED.*, 1913, **12**, 420.

A REPORT ON FORTY CASES OF ACUTE ARTHRITIS TREATED BY THE INTRAVENOUS INJECTION OF FOREIGN PROTEIN *

RUSSELL L. CECIL, M.D.
NEW YORK

Nonspecific vaccination in the treatment of infections is not a new procedure. As far back as 1893, Rumpf¹ treated typhoid fever patients with a *B. pyocyaneus* vaccine and claimed to have obtained excellent results. Von Wagner² found that paretics treated with tuberculin showed marked improvement. Hiss and Zinsser³ used extracts of rabbit's leukocytes in various infectious diseases, especially pneumonia, and were favorably impressed with the results. Some of the German writers have employed boiled milk subcutaneously in infections, and report success. More recently Schaefer's mixture of many bacteria has been widely advertised in the treatment of various diseases, more particularly of arthritis.

The practice of intravenous injection of foreign proteins is a comparatively recent one, and may be said to have originated with the intravenous injection of typhoid vaccine in the treatment of typhoid fever. Ichikawa⁴ was one of the first to use the intravenous method of vaccination. By giving sensitized typhoid vaccine intravenously he observed that cases not only of typhoid but also of paratyphoid fever often showed marked improvement after the injection, the temperature sometimes dropping to normal and remaining there. Gay and Chickering,⁵ Miller and Lusk⁶ and others have reported favorably on the results of intravenous injections of typhoid vaccine in typhoid fever. Kraus⁷ obtained similar results in typhoid fever by using colon bacillus vaccine intravenously. Lüdke⁸ substituted albumose for vaccine and obtained the same sort of a crisis in many cases. Psoriasis and certain other skin diseases have been successfully

* Submitted for publication Aug. 1, 1917.

* From the Second Medical Service of Bellevue Hospital, Cornell Medical School.

1. Rumpf: Deutsch. med. Wchnschr., 1893, **19**, 987.
2. Von Wagener, J.: Wien. med. Wchnschr., 1909, **59**, 2124.
3. Hiss, P., and Zinsser, H.: Jour. Med. Research, 1908, **19**, 321.
4. Ichikawa, S.: Ztschr. f. Immunitätsf., 1915, **23**, 32.
5. Gay, F., and Chickering, H.: THE ARCHIVES INT. MED., 1916, **17**, 303.
6. Miller, J., and Lusk, F.: Jour. Am. Med. Assn., 1916, **66**, 1756.
7. Kraus, R.: Wien. klin. Wchnschr., 1915, **28**, 29.
8. Lüdke, H.: München. med. Wchnschr., 1915, **62**, 321.

treated by a number of dermatologists with intravenous injections of serum.

The application of intravenous vaccination to the various forms of arthritis is comparatively recent. Miller and Lusk,⁹ in 1916, reported a series of cases of acute and chronic arthritis in which the patients were treated by intravenous injections of typhoid bacilli and of secondary proteose, and obtained excellent results in a majority of the cases. In a second paper Miller and Lusk⁹ report 85 cases of arthritis in which the patients were treated by the intravenous injection of typhoid vaccine. Forty-five of these were cases of acute arthritis, and 33 of the patients had already been treated with salicylates, without benefit, except in 4 cases. Twenty-nine out of the 45, after receiving one to four doses of vaccine, recovered in one to five days; 8 showed marked improvement, 6 moderate improvement, and 2 no improvement. The 4 gonococcus cases in this series did not respond brilliantly to the vaccine. There were nine relapses in the acute series. Of 12 cases of subacute arthritis, 10 cleared up in three to five days, and the other 2 patients improved. Nineteen chronic but still active cases were treated, in 10 of which the patients showed improvement. Culver¹⁰ reports a series of 31 gonococcus arthritis cases, in 28 of which the patients either recovered or greatly improved after intravenous injection of gonococcus, meningococcus or colon vaccine. Matthers¹¹ reports favorably on various infections, including acute arthritis, treated by intravenous injections of vaccine and pure protein. Manier, Petersen and Jobling¹² have treated 13 patients with arthritis by intravenous injections of secondary proteoses. Three of the cases were acute, 3 subacute and 7 chronic. Of the acute cases, 2 cleared up promptly after the injections, while in the third, a gonococcus arthritis, the patient was not relieved. In the 3 subacute cases the patients all recovered rapidly after vaccination. In the chronic series there was complete relief in 3, marked improvement in 3 and no change in 1. The reports on this subject, though not numerous, have been so favorable that it seemed desirable to give the method a trial.

Classification of Cases.—The present study is based on 40 cases of acute arthritis in which the patients were treated in the medical wards of Bellevue Hospital. These cases may be classified as follows: rheumatic fever, 26; acute toxic arthritis, 7; gonococcus arthritis, 7.

9. Miller, J., and Lusk, F.: Jour. Am. Med. Assn., 1916, **67**, 2010.

10. Culver, H. B.: Quoted by Jobling, THE ARCHIVES INT. MED., 1917, **19**, 1042.

11. Matthers, M.: Quoted by Jobling, THE ARCHIVES INT. MED., 1917, **19**, 1042.

12. Jobling, J. W.: Jour. Am. Med. Assn., 1916, **66**, 1753; THE ARCHIVES INT. MED., 1917, **19**, 1042.

Of the 40 patients, 30 were male and 10 female. The average age of the rheumatic fever patients was 26 years; of the acute toxic arthritis series, 42; of the gonococcus arthritis series, 27. In the rheumatic series 12 patients had been subject to attacks of tonsillitis or sore throat; 15 had had previous attacks of rheumatic fever. In the acute toxic arthritis series only 1 gave a history of tonsillitis and 1 had had a previous attack of the same illness.

Complications.—Tonsillitis was noted as a complication in 8 of the rheumatic fever series; sore throat or coryza in 7 cases; rheumatic endocarditis was noted in 15 cases; pyorrhea was present in 3 of the acute toxic arthritis cases; tonsillitis twice, and pneumonia with empyema, once. In the gonococcus series, 6 of the cases were associated with gonococcus urethritis and 1 with gonococcus vaginitis. In 1 case gonococcus iritis was also present.

The rheumatic fever cases varied in severity. Some of the patients were quite ill, with high fever and profuse sweats. All of the rheumatic fever series were cases of polyarthritis as were also the acute toxic arthritis cases. All but one case of the gonococcus series (Case 40) were polyarticular, but usually the latter changed to a monarticular type.

The temperature on admission varied from 98 to 101 F., but in a few cases it was as high as 102 to 103. The leukocyte count on admission varied from 7,000 to 22,000. Two of the rheumatic fever patients and one of the gonococcus patients had positive Wassermann reactions, but none of these showed any clinical signs of syphilis. The gonococcus fixation test was positive in five out of the seven cases of gonococcus arthritis.

The Vaccine.—Typhoid vaccine has been used almost exclusively in this study. The New York City Board of Health vaccine was employed. It is made up in the usual way from a number of strains of *B. typhosus*. In five of the gonorrheal cases a polyvalent gonococcus vaccine (also New York City Board of Health) was used.

Administration of Vaccine.—The vaccine in every case was given intravenously. The vein used was the median basilic and the injection was made with a small tuberculin syringe. The vaccine was diluted so that 1 c.c. = 100 million bacteria. In none of the cases was there any local reaction. The dose of vaccine administered varied from 30 to 100 million, the usual dose being 40 to 80 million. By a mistake in technic, 400 to 500 million bacteria were given to three patients (Cases 24, 29 and 31). The reaction produced by these large doses was little if any more severe than that caused by small doses, and the therapeutic result was no better. The average number of doses of vaccine administered in the rheumatic fever series was almost two (1.8 per

cent.). In the acute toxic arthritis series, the average dose was 1.5; in the gonococcus series 5.5. The reason for this difference in the number of doses was that in the rheumatic fever cases we were able to resort to salicylates if one or two doses of the vaccine proved insufficient to produce recovery; whereas in the gonococcus series

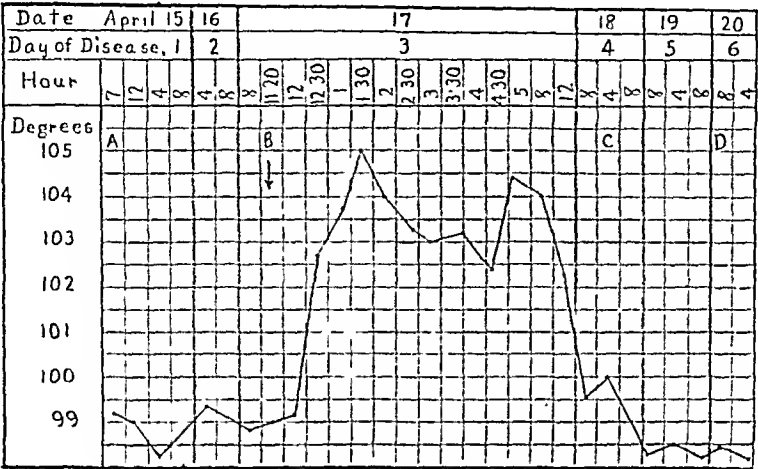


Chart 1.—Case 2. Rheumatic fever. Intravenous injection of typhoid vaccine. The temperature curve shows the secondary rise which is often present. A, admission; B, 40 mg. typhoid vaccine intravenously; C, patient better; D, no pain.

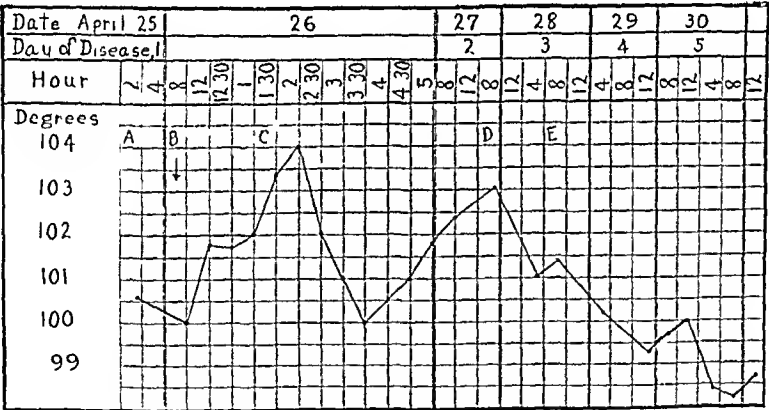


Chart 2.—Case 4. Rheumatic fever. Intravenous injection of typhoid vaccine. Secondary rise of temperature occurs late. A, on admission; B, 50 mg. typhoid vaccine intravenously at 12:00; C, chill at 12:30; D, better; E, no pain.

patients were in the hospital for a number of weeks, and there was no other form of medication which seemed of any particular value.

Reaction Caused by Vaccines.—The typical reaction produced by an intravenous injection of typhoid or gonococcus vaccine may be described as follows: In twenty minutes to one hour after the injection the patient has a severe shaking chill, which lasts fifteen to thirty min-

utes, and is accompanied by a rapid rise in temperature. In two to three hours the temperature may have risen 2 to 5 degrees (Charts 1, 2 and 3). In a considerable number of cases there is a secondary rise in temperature, usually not so high as the primary, which may show

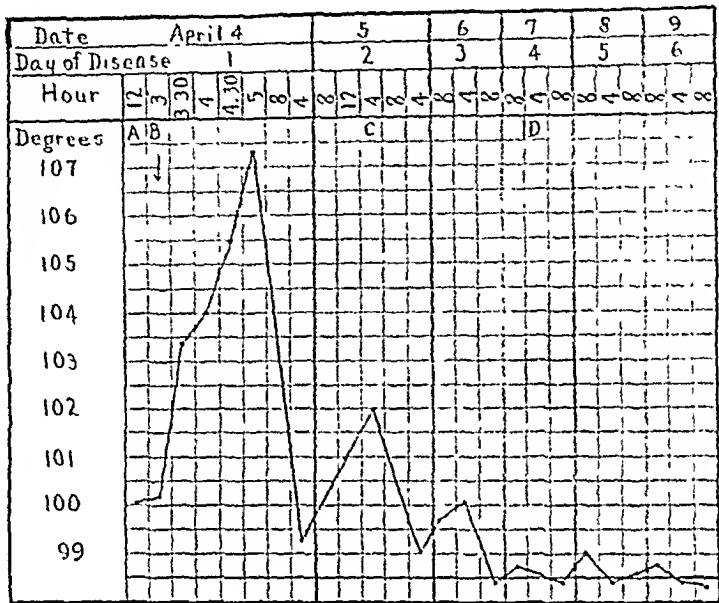


Chart 3.—Case 7. Rheumatic fever. Chart shows extreme rise of temperature following intravenous injection of typhoid vaccine. A, admission; B, 40 mg. typhoid vaccine intravenously; C, much better; D, no pain.

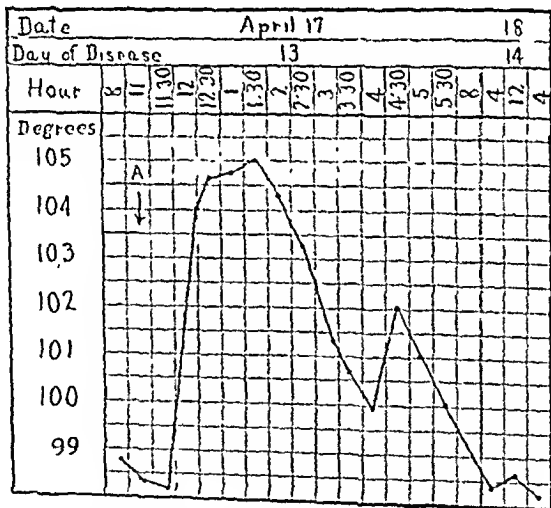


Chart 4.—Case 38. Gonococcus arthritis. Chart shows marked rise of temperature following intravenous injection of gonococcus vaccine. Reaction similar in all respects to typhoid vaccine reaction. A, 100 mg. gonococcus vaccine intravenously at 11:00.

itself in two to twelve hours (Charts 1 and 2). In some instances there is nausea and vomiting and quite a number of patients have a severe headache. In the course of the next three to six hours the temperature drops and by the following day it is usually normal.

Effect of Vaccine on Leukocyte Count.—Immediately after the injection of the vaccine, there is a slight fall in the leukocytes, followed in a short time by a rapid rise. In the course of two hours after the injection the leukocyte count may be four or five times the normal. For instance, in one case the count was 47,000, with 95 per cent. polynuclear neutrophils. The count rapidly returns to normal, though in Case 15 it was still 22,600 forty-eight hours after the injection. In five cases in which the leukocytes were counted one to two hours after the injection of vaccine the average count was 26,000.

Effect of Vaccine on Symptoms.—During the febrile period the patient nearly always feels better, and this relief from pain usually lasts twenty-four to forty-eight hours. The heat, redness and swelling may disappear entirely from the joints and complete and permanent recovery take place. More often there is a return of symptoms, which

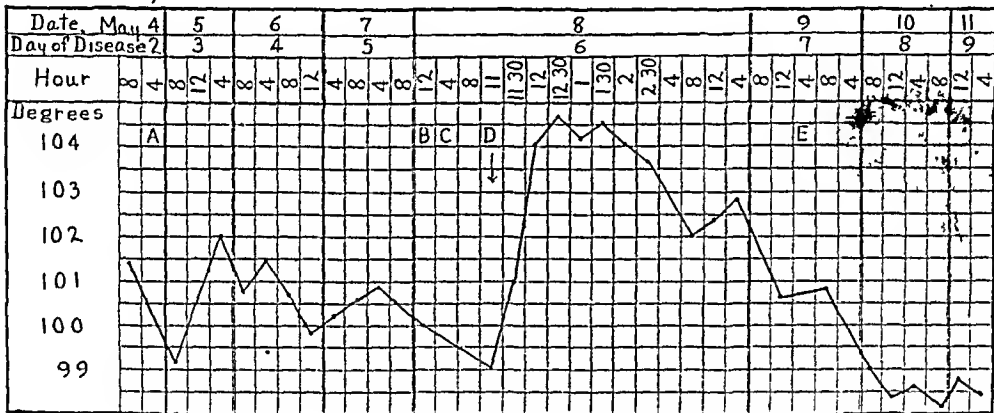


Chart 5.—Case 22. Pneumonia and empyema, followed by acute arthritis (rheumatic fever?); no relief from salicylates; immediate recovery after one intravenous injection of typhoid vaccine. A, sodium salicylate, 20 grains every four hours; B, no better; C, salicylates discontinued; D, 60 mg. typhoid vaccine intravenously at 11:00; E, pain and swelling gone; feels fine.

are usually not so severe as those before vaccination, and a second dose of vaccine may be necessary to bring permanent relief. On account, however, of the discomfort associated with these reactions to the vaccine, it seemed preferable in many of our cases to start the patients on salicylates, if one or two doses of the vaccine did not produce complete recovery. Twenty grains of salicylic acid or sodium salicylate, with 40 grains of sodium bicarbonate were given every two to four hours, depending on the severity of the symptoms, and continued until the patient was free from pain.

Contraindications.—In the present series we have considered severe cardiac or renal disease as contraindications to the use of intravenous vaccination. In markedly prostrated patients the vaccine is badly

borne, but may prove of much benefit. Such patients should be started with a small dose of 30 or 40 million bacteria.

Results.—Of the 33 cases of rheumatic fever and nonspecific arthritis studied, 13 (or about 40 per cent.) of the patients recovered completely in two to ten days without the aid of salicylates. (By recovery is meant the ability to be up and about the wards and free from pain.) The remaining 20 patients (or 60 per cent.) of the series received salicylates at some period during their attack. In 2 cases (Cases 22 and 33) the patients received salicylates without benefit for a number of days *before* the vaccine was tried. Of these 2 patients, 1 made a complete recovery after vaccination (Chart 5), and the other was much improved by it. The remaining 18 patients received vaccines first and salicylates afterward. Of these 18, three obtained no benefit from the vaccine; the remaining 15 improved, but were not completely cured until salicylates were given (Chart 6).

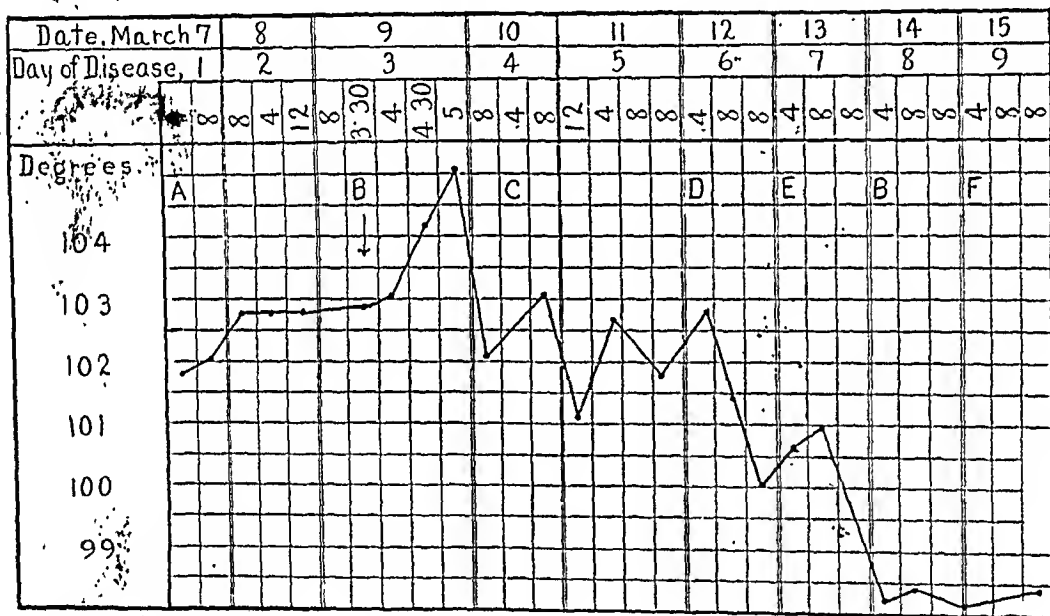


Chart 6.—Case 21. Rheumatic fever. Improved after vaccination, but relapsed. Rapid recovery after administration of salicylates: A, on admission; B, 40 mg. typhoid vaccine intravenously; C, better; D, relapse; E, salicylates started; F, better.

A noteworthy fact was that while the pain disappeared from the joints in many of these vaccinated patients, muscular pain persisted, particularly in the back or neck, and it was for these muscular pains that salicylates were resorted to.

The seven patients with gonococcus arthritis all made slow improvement during their stay in the hospital and appeared to be influenced little, if any, by the vaccine. Two of the patients received typhoid vaccines and the remainder gonococcus vaccine. There was no difference observed in the character of the reaction produced (Chart 4) or in the therapeutic value of the two vaccines. The gonococcus patients

CASES OF ACUTE ARTHRITIS—

Case	Age	Sex*	Clinical Diagnosis	Complications	Previous illness	White Blood Cells
1. G. M.	17	♀	Rheumatic fever	Cervical adenitis; endocarditis	Rheumatic fever; tonsillitis
2. K. H.	24	♀	Rheumatic fever	Anemia	Measles; scarlet fever
3. M. C.	14	♂	Rheumatic fever	Tonsillitis; acute nephritis	Tonsillitis
4. M. D.	24	♀	Rheumatic fever	Endocarditis	Rheumatic fever
5. M. H.	55	♀	Acute arthritis	Hemiplegia; angina pectoris?
6. G. G.	21	♂	Rheumatic fever	Tonsillitis; endocarditis	Rheumatic fever	21,000 Polys. 69%
7. M. M.	42	♀	Acute arthritis	Chronic tonsillitis; pyorrhea; endocarditis	Tonsillitis
8. Z. T.	22	♂	Rheumatic fever	Pharyngitis; pyorrhea
9. G. C.	27	♂	Rheumatic fever	Tonsillitis	Rheumatic fever
10. M. R.	40	♂	Acute arthritis	Large tonsils; pyorrhea	Acute arthritis
11. W. K.	34	♂	Rheumatic fever	Tonsillitis; endocarditis	Gonorrhea 6 years ante
12. A. K.	57	♂	Rheumatic fever	Tonsillitis; endocarditis; pyorrhea	Tonsillitis; rheumatic fever	7,000
13. B. S.	46	♂	Acute arthritis	Pyorrhea; bronchitis; delirium tremens	Gonorrhea 20 years ante	16,800 Polys. 76%

Cases in which Vaccine Was Supplemented by Salicylates

14. P. B.	24	♂	Rheumatic fever	Furuncles; endocarditis	Frequent sore throat	10,600 Polys. 70%
15. J. F.	40	♂	Rheumatic fever	Sore throat	Rheumatic fever, 6 attacks	22,600 Polys. 81%
16. B. Sm.	19	♀	Rheumatic fever	Tonsillitis	Appendicitis; pneumonia; frequent sore throat
17. A. H.	21	♂	Rheumatic fever	Endocarditis; broncho-pneumonia	Rheumatic fever; frequent sore throat	17,700 Polys. 82%
18.	26	♂	Rheumatic fever	Endocarditis; coryza; pyorrhea	Rheumatic fever, 3 attacks
19. E. L.	47	♂	Acute arthritis	Vincent's angina	Gonorrhea 3 times; syphilis
20. M. P.	37	♀	Rheumatic fever	Pyorrhea	Rheumatic fever, 3 times	14,000 Polys. 81%
21. D. H.	22	♀	Rheumatic fever	Sore throat 1 week before	Measles
22. R. L.	25	♂	Acute arthritis	Lobar pneumonia; empyema	19,000 Polys. 87%

* ♂ denotes male; ♀ female.

—TREATED WITH TYPHOID VACCINE

Wasser- mann	Gonococcus Fixation	Number of Injec- tions of Vaccine	Result	Remarks
Negative	Negative	1, 50 million	Complete recovery in 48 hours	
.....	Negative	1, 40 million	Complete recovery in 4 days	
.....	1, 30 million	Complete recovery in 5 days	Herpes labialis after vaccine
Negative	Negative	1, 50 million	Complete recovery in 3 days	Herpes labialis
.....	2, 50 million each	Complete recovery in 5 days	Herpes labialis
Negative	Negative	2, 40 million each	Complete recovery in 6 days	Blood culture sterile
.....	Negative	1, 40 million	Complete recovery in 10 days	
Negative	Negative	2, 50-60 million	Complete recovery in 10 days	Greek; history obtained with dif- ficulty
Negative	Negative	3, 40-60 million	Much improved (9 days)	Free from symptoms 24 hours after each injection, but re- lapsed twice
Negative	Negative	1, 80 million	Complete recovery in 5 days	Uric acid in blood = 4 mg. per 100 c.c.
.....	1, 75 million	Complete recovery in 6 days	
Negative	Negative	2, 60-70 million	Complete recovery in 6 days	
Negative	Negative	1, 100 million	Complete recovery in 3 weeks	Delirium tremens appeared 2 hours after vaccination and lasted 4 days

Cases in which Vaccine Was Supplemented by Salicylates

Negative	Negative	2, 50 million each	Improved after vaccine	Recovery under salicylates; blood culture sterile
.....	Negative	1, 60 million	Much improved after vaccine	Relapse 3 days after vaccination; salicylates; recovery
.....	1, 70 million	Recovery in 2 days except for backache	Salicylates for backache
Negative	1, 40 million	No improvement	Blood culture sterile; on 4th day pneumonia; salicylates started; complete recovery
Negative	Negative	4, 60-70 million	Improved temporarily after each dose	Blood culture sterile; two relapses; salicylates; recovery
Positive	Negative	1, 50 million	Improved	Salicylates; complete recovery
.....	Negative	1, 60 million	Much improved	Salicylates; complete recovery
.....	1, 40 million	Much better day after vaccination	Relapse; salicylates; complete re- covery
.....	Negative	1, 60 million	Complete recovery	Patient had received large doses of salicylates without benefit

CASES OF ACUTE ARTHRITIS TREATED—

Cases in which Vaccine Was Supplemented by Salicylates

Case	Age	Sex*	Clinical Diagnosis	Complications	Previous Illness	White Blood Cells
23. P. H.	46	♂	Rheumatic fever	Endocarditis; pyorrhea	Gonorrhea, 20 years ante; rheumatic fever
24. F. S.	26	♂	Rheumatic fever	Endocarditis	Rheumatic fever; sore throats	18,000 Polys. 87%
25. J. O.	22	♀	Rheumatic fever	Tonsillitis; adenitis	Rheumatic fever; tonsillitis
26. J. M.	13	♂	Rheumatic fever	Endocarditis; pericarditis	12,800 Polys. 77%
27. H. H.	43	♂	Acute arthritis	Sore throat 2 weeks before admission	Gonorrhea denied
28. J. R.	28	♂	Rheumatic fever	Coryza; endocarditis	Rheumatic fever; gonorrhea at 16
29. P. O.	32	♂	Rheumatic fever	Endocarditis; paroxysmal tachycardia	Rheumatic fever; sore throats	7,200 Polys. 82%
30. G. A.	22	♂	Rheumatic fever	Sore throat; endocarditis
31. M. Y.	24	♂	Rheumatic fever	Sore throat	Frequent sore throat
32. N. P.	22	♂	Rheumatic fever	Tonsillitis; endocarditis	Rheumatic fever; tonsillitis	11,800 Polys. 84%
33. L. A.	28	♂	Rheumatic fever	Endocarditis	Gonorrhea 5 years ante	20,200 Polys. 82%

Gonococcus Arthritis Treated with Gonococcus and Typhoid Vaccine Intravenously

34. J. M.	27	♂	Gonococcus arthritis	Gonococcus urethritis	Several attacks of gonorrhea	7,800 Polys. 57%
35. J. B.	19	♂	Gonococcus arthritis	Gonococcus urethritis	Chorea; rheumatic fever	10,800 Polys. 75%
36. F. G.	42	♂	Gonococcus arthritis	Gonococcus urethritis and iritis
37. A. S.	28	♀	Gonococcus arthritis	Gonococcus vaginitis	Rheumatism 2 years ante
38. C. E.	21	♂	Gonococcus arthritis	Gonococcus urethritis	Gonorrhea 2 times	8,000 Polys. 85%
39. R. F.	37	♂	Gonococcus arthritis	Gonococcus urethritis	Gonorrhea 2 times
40. J. V.	21	♂	Gonococcus arthritis	Gonococcus urethritis	13,600 Polys. 83%

* ♂ denotes male; ♀ female.

—WITH TYPHOID VACCINE—(Continued)

Cases in which Vaccine Was Supplemented by Salicylates

Wassermann	Gonococcus Fixation	Number of Injections of Vaccine	Result	Remarks
Positive	Negative	1, 60 million	Improved	Herpes labialis (severe); salicylates; recovery
Negative	Negative	1, 500 million	No improvement	Salicylates; recovery
Positive	Negative	2, 50-70 million	Almost complete recovery	Salicylates given during last 2 days in hospital for muscular pains
Negative	1, 30 million	Improved	Blood culture sterile; vaccine not repeated on account of heart; salicylates; recovery
.....	Negative	3, 40 million each	Temporary relief from vaccine	Salicylates for 2 weeks; much improved
.....	Negative	1, 75 million	No improvement	Salicylates; recovery
Negative	Negative	2, 400 million each	Improved	Blood culture sterile; salicylates; recovery
Negative	Negative	7, 20-60 million	Improved but relapsed	Blood culture sterile; salicylates; recovery
Negative	Negative	2, 400 million each	Improved	Salicylates given for pain in back; recovery
.....	2, 40 million each	Recovery, but relapsed 2 days after discharge	Blood culture sterile; salicylates for relapse; recovery
Negative	Negative	3, 20-40 million	Much improved	Blood culture sterile; salicylates for 9 days; no improvement; then vaccine

Gonococcus Arthritis Treated with Gonococcus and Typhoid Vaccine Intravenously

Negative	Negative	4, 40-60 million (typh. vac.)	Much improved	In hospital 5 weeks; left with some stiffness in back; otherwise O.K.
Negative	Weakly pos.	7, (3 typh. vac., 4 gon. vac.)	Improved	In hospital 2 months; when discharged, walked with limp and had fluid in both knees
Negative	Positive	8, 30-175 million (typh. vac.)	Much improved	In hospital 6 weeks; still having occasional pain when discharged, but practically cured
Negative	Positive	5, (2 typh. vac., 2 gon. vac.)	Improved	In hospital 7 weeks; when discharged ankle was still sore, but could walk on it
Negative	Negative	5, 50-100 million (gon. vac.)	Much improved	Herpes labialis; in hospital 5 weeks; still limping when he left hospital
Negative	Positive	4, 60-100 million (gon. vac.)	Improved	In hospital 3 weeks; left hospital on crutches; still lame 1 month later
Positive with cholesterolin antigen	Positive	5, 60-100 million (gon. vac.)	Improved	In hospital 5 weeks; still lame when he left hospital

remained in the hospital from three to eight weeks. The average duration of their stay in the hospital was five and one-half weeks. They all left the hospital in about the same stage of improvement; that is, with one or two joints still stiff and somewhat painful on motion, but with no signs of active infection in them. The injection of vaccine seemed to give relief for twenty-four hours or more; then the pain in the joints would return to the previous state.

Other Effects of Vaccine.—No unpleasant effects were noted from the vaccines other than the chill and fever and the constitutional symptoms above described. Five of the patients developed herpes labialis, apparently as the result of the vaccine, and one alcoholic patient had delirium tremens, which developed on the day after the vaccine was given.

DISCUSSION

The reaction produced by the intravenous injection of typhoid or gonococcus vaccine is usually quite rigorous and not a particularly pleasant experience for the patient. The question which immediately comes up is whether the results obtained by the vaccine are sufficiently brilliant to justify the use of this rather heroic measure. While it is true that in 40 per cent. of our cases of rheumatic fever (including the cases of acute arthritis) the patient recovered without the use of salicylates, it must be remembered that rheumatic fever is usually a self-limited disease and that in many instances the patient would make a rapid recovery even if no medication were given. From my own experience with thirty-three patients treated by this method I feel that salicylic acid is still our best weapon against rheumatic fever, and that the intravenous injection of vaccine or of foreign proteins should be employed only after salicylates have been ineffective.

As for the seven gonococcus cases, the vaccine seemed to have no permanent effect and, so far as I could see, exercised no influence one way or the other on the course or outcome of the disease. Miller reports similar results with his gonococcus arthritis cases. These are always difficult cases to handle, and appear to run their course in spite of all local or constitutional treatment.

It is interesting to speculate as to what causes the benefit which many of these patients received from intravenous vaccination. A number of explanations have been given. The leukocytosis may be responsible for their recovery, as emphasized by Gay¹³ and his co-workers. It seems more probable, however, that the rise in temperature is a more important factor; certainly we never see improvement in these cases of arthritis unless there is an accompanying pyrexia. In a case of chronic arthritis, which is not included in the present study, I gave the patient

13. Gay, F., and Claypole, E.: *THE ARCHIVES INT. MED.*, 1914, **14**, 662.

several intravenous injections of an autogenous *Streptococcus viridans* vaccine. The injections were followed by a slight malaise and headache, but there was practically no rise in temperature, and the vaccine had no effect whatever on the course of the disease.

Jobling and Petersen¹⁴ have shown that the intravenous injection of bacteria, protein split products, trypsin and kaolin, is almost invariably followed by more or less marked mobilization of serum protease and esterase. There is also a distinct rise in the anti-ferment titer of the serum following such injections. As Jobling¹² says, however, these serum changes are more or less temporary and do not explain the permanent recovery of patients treated by intravenous injections of vaccine and other proteins.

For the present we must admit that no thoroughly satisfactory explanation can be given of this interesting phenomenon. Practically speaking, we have at our disposal a rather heroic therapeutic measure, at times quite efficient, but likely to prove dangerous in the hands of inexperienced workers. For the present we should recommend its use only after salicylates and other well established methods of treating arthritis have failed.

CONCLUSIONS

In forty cases of acute arthritis the patients have been treated by intravenous injections of typhoid or gonococcus vaccine. Thirteen of these patients, or 32 per cent., made a rapid recovery without recourse to any other treatment. Of the remaining twenty-seven cases, all but two patients showed improvement while receiving the vaccine. Twenty out of the twenty-seven, however, received salicylates before complete recovery took place. In the seven cases of acute gonococcus arthritis all of the patients showed gradual improvement under vaccine, but it was impossible to say how much of a factor the vaccine was in these cases.

The reaction produced by the vaccine is usually severe, consisting of a chill, with rapid rise in temperature, headache, and often nausea and vomiting. During this reaction there is a well-marked leukocytosis. Both the temperature and the leukocytes usually return to normal in a few hours.

This method of treatment is undoubtedly efficient in many cases of acute arthritis; but it is unpleasant for the patient, and may be dangerous when administered to improperly selected patients.

For the present, its use is recommended only in carefully selected cases, after salicylates and other well established methods of treating arthritis have failed.

123 East Sixty-Second Street.

14. Jobling, J. W., and Peterson, W.: Jour. Exper. Med., 1915, **22**, 590, 597, 603, 141.

BLOOD SUGAR IN HYPERTHYROIDISM*

W. DENIS, PH.D., AND J. C. AUB, M.D.

WITH THE ASSISTANCE OF

A. S. MINOT, A.B.

BOSTON

Since, and even before, the advent of modern methods for the determination of blood sugar, the spontaneous glycosuria so frequently observed in patients suffering from hyperthyroidism has led several investigators to make studies on blood sugar in this disease. These studies have led to conflicting results. Tachaw¹ and Flesch² found an alimentary hyperglycemia in some cases, but not in others. In forty cases the latter investigator reported not a single instance of spontaneous hyperglycemia. On the other hand, Geyelin,³ from a study of twenty-seven cases of hyperthyroidism, concludes that an unmistakable hyperglycemia can be demonstrated in 90 per cent. of the moderate and severe cases, while even in mild types of the disease an alimentary hyperglycemia (two hours after 100 gm. of glucose) could frequently be demonstrated. In view of this lack of uniformity in the results reported, it has seemed worth while to carry out a series of experiments dealing with the effect produced by carbohydrate ingestion on persons suffering from hyperthyroidism. Coincident with these experiments we have made observations on the gaseous metabolism of these patients, with the idea of establishing, if possible, some relation between the increase in metabolism found in this condition and the effect produced on the blood sugar level by the ingestion of carbohydrate. The blood sugar determinations were made by the method of Lewis and Benedict as modified by Myers and Bailey,⁴ 2 to 4 c.c. of blood being used for each determination. Qualitative and quantitative determinations of sugar in urine were made by Benedict's⁵ methods.

Method of Procedure.—Between 7 and 8 a. m., the patient who had received no food since 5 o'clock on the previous afternoon was given 100 gm. of glucose

* Submitted for publication July 27, 1917.

* From the Chemical Laboratory and Medical Service of the Massachusetts General Hospital.

1. Tachaw: Deutsch. Arch. f. klin. Med., 1911, **114**, 445.

2. Flesch: Beitr. z. klin. Chir. (Bruns'), 1912, p. 236.

3. Geyelin: The Carbohydrate Metabolism in Hyperthyroidism as Determined by Examination of Blood and Urine, THE ARCHIVES INT. MED., 1915, **16**, 975.

4. Myers and Bailey: Jour. Biol. Chem., 1916, **24**, 147.

5. Benedict, S. R.: Jour. Biol. Chem., 1909, **5**, 485, and 1911, **9**, 57.

(in lemonade or "postum"), 50 gm. of bread, and 20 gm. of butter. Just previous to this meal a sample of urine was secured and 5 c.c. of blood were taken by venepuncture. Samples of blood and urine were then obtained at hourly intervals, from three to four samples of blood being taken from each patient.

The method used for the determination of the basal metabolism was that described by Benedict.⁶ All patients were fasting for approximately fourteen hours before the observation, and were at complete rest both during and for at least one-half hour before the test. Three periods of ten minutes each were run on each subject when possible, but in some cases the nervous instability of the patients prevented our securing more than two satisfactory observations.

The surface area of the subjects was estimated by the "height-weight formula" of Du Bois.⁷ For ease of interpretation, we have expressed the basal metabolism data in terms of percentage variation from the normal, the normal standards used being those given by Aub and Du Bois.⁸

Recent work points to the view that the increase in basal metabolism observed in cases of uncomplicated hyperthyroidism may be regarded as a functional test to indicate the degree of toxicity at the time of observation. The expression of the basal metabolism in terms of a percentage change from normal is therefore used in this paper on the assumption that it is to be interpreted as furnishing a numerical index of the severity of the case.⁹ The patients used belonged to a series of cases of hyperthyroid now being investigated by Means and Aub¹⁰ and, in accordance with the average results obtained by these investigators, we have considered mild cases to give an average value of +43 per cent., moderately severe cases +53 per cent. and severe cases +76 per cent. Any determination more than +15 per cent. should be considered abnormal. We are aware of the fact that the clinical notes do not invariably check with the metabolism data, the reason for this discrepancy being the fact that the metabolism figures represent the condition of the patient at the time of observation, while the clinical diagnosis represents the general impression gained by observation of the patient over a period of some weeks.

Before making any observations on patients we have administered our "test breakfast" to sixteen normal persons, seven women and nine men. The female subjects were, with one exception (Mrs. D. K., a surgical patient), nurses or laboratory workers. The male subjects were physicians or medical students. All were apparently in good health and free from any suspicion of hyperthyroidism. The results on this group of subjects are presented in Table 1.

In these normal subjects the "fasting" blood sugar shows a minimum value of 0.090 per cent., a maximum of 0.12 per cent., and an average value of 0.10 per cent. An experience of more than a year with the analytic method employed (during which time several hundred samples of human blood were examined) leads us to suspect that the maximum value obtained, 0.12 per cent., is distinctly above the values

6. Benedict, F. G.: *Deutsch. Arch. f. klin. Med.*, 1912, **107**, 156.

7. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate the Approximate Surface Area If Height and Weight Be Known, *THE ARCHIVES INT. MED.*, 1916, **17**, Part 2, p. 863.

8. Means, J. H., Aub, J. C., and Du Bois, E. F.: The Effect of Caffein on the Heat Production, *THE ARCHIVES INT. MED.*, 1917, **19**, 832.

9. Du Bois, E. F.: Metabolism in Exophthalmic Goiter, *THE ARCHIVES INT. MED.*, 1916, **17**, 915.

10. Means, J. H., and Aub, J. C.: Preliminary report in press, *Jour. Am. Med. Assn.*

ordinarily obtained in normal cases, the sugar values for which are, according to our experience, 0.085 to 0.110 per cent., a finding in close agreement with the normal figures for human blood reported by Lewis and Benedict and by Myers and Bailey. As, however, the subject whose blood gave this high value was, to the best of our knowledge, in good health, we do not feel justified in excluding him from the series.

TABLE 1.—NORMAL SUBJECTS

Name	Sex*	Age, Yrs.	Weight, Kg.	Blood Sugar, per Cent.				Remarks
				Fast-ing	One Hour	Two Hours	Four Hours	
Bd.	♀	24	53	0.100	0.110	0.090	Trace of sugar present in urine passed 2 hours after breakfast
Bl.	♀	24	...	0.100	0.120	0.110	No glycosuria
Ds.	♀	37	91	0.110	0.110	0.086	Trace of sugar present in urine passed 2 hours after breakfast
M.	♀	22	53	0.090	0.086	0.088	No glycosuria
T.	♀	24	71	0.090	0.090	0.100	No glycosuria
L.	♀	30	132	0.090	0.110	0.110	0.089	Trace of sugar in urine passed 2 and 4 hours after breakfast
DK.	♀	31	...	0.110	0.140	0.110	0.110	Trace of sugar in urine passed 4 hours after breakfast
Ab.	♂	27	60	0.110	0.094	0.103	No glycosuria
Sn.	♂	27	68	0.096	0.097	0.120	No glycosuria
C.	♂	29	64	0.120	0.119	0.122	No glycosuria
Ts.	♂	25	77	0.113	0.085	0.110	No glycosuria
Sd.	♂	26	74	0.099	0.104	0.103	No glycosuria
O.	♂	27	72	0.100	0.084	0.109	No glycosuria
B.	♂	26	70	0.110	0.100	0.097	No glycosuria
As.	♂	26	67	0.100	0.100	0.100	No glycosuria
Ta.	♂	25	73	0.100	0.100	0.090	No glycosuria

An inspection of Table 1 shows that in the case of most normal persons the ingestion of 100 gm. of glucose and 50 gm. of bread causes no increase in blood sugar two hours, or even one hour after breakfast. Two exceptions to this statement are to be noted: Miss Bd. and Miss L. both show an unmistakable increase which had not disappeared in two hours. Inquiry revealed the fact that both of these nurses were engaged in work of an exacting nature and were probably in need of a vacation. As will be noted, both showed a slight glycosuria. This interpretation is in line with the findings of Graham¹¹ who, in a series of experiments on himself, demonstrated the fact that when in good condition the blood sugar regains its original level one to one and one-

11. Graham, G.: Jour. Physiol., 1916, 50, 285.

half hours after ingestion of 100 gm. of glucose, whereas under conditions which cause fatigue, three to four hours elapse before the fasting blood sugar level is again reached.

In Table 2 are presented the results obtained by taking single samples of blood from fasting patients suffering from various grades of hyperthyroidism. Of the thirteen cases in this series, only five patients showed blood sugar values above normal (on the assumption that any figure above 0.110 per cent. may be considered to indicate hyperglycemia). These patients were all outpatient cases, who before venipuncture had been subjected to several periods of observation on

TABLE 2.—ANALYSES OF BLOOD IN HYPERTHYROIDISM

Num-ber	Blood Sugar, per Cent.	Pulse	Weight, Kg.	Basal Metabo-lism, per Cent. Vari-ations from Normal	Remarks
123	0.117	157	48.0	+89	Woman, aged 29 years. Thyrotoxicosis; very toxic
120	0.122	130	53.0	+67	Woman, aged 45 years. Severe case; very toxic
53	0.114	96	65.5	+60	Man, aged 27 years. Very toxic after 6 months of rest
77	0.129	146	50.0	+47	Woman, aged 29 years. Very toxic; metabo-lism observation not very satisfactory; very much excited by venesection
114	0.080	108	55.0	+47	Woman, 41 years old. Toxic; subsequent rapid recovery
89	0.102	102	64.0	+35	Woman, aged 23 years. Severe thyrotoxicosis of 1½ years' duration
71	0.083	113	68.0	+40	Woman, aged 37 years. Mildly toxic case
66	0.117	118	49.6	+33	Woman, aged 27 years. Mildly toxic case
72	0.097	106	53.5	+30	Woman, aged 18 years. Mild thyrotoxicosis
96	0.102	101	47.0	+18	Woman, aged 35 years. Mildly toxic. Recur-rence following operation
18	0.103	86	48.0	+14	Woman, aged 31 years. Mildly toxic; chronic type
92	0.117	94	46.6	+12	Woman, aged 20 years. Large thyroid; not toxic
105	0.101	100	55.5	+ 9	Woman, aged 43 years. Questionable case; probably not hyperthyroid

the respiration apparatus. It is, therefore, conceivable that an emo-tional factor might be involved in the cases in which hyperglycemia was noted, and, in fact, the observation was made that in Case 77, the patient who gave the highest blood sugar value of the series, was much excited by the respiration observations and by the prospect of veni-puncture. Although this series of cases is small, it is obvious that these single blood sugar observations made on fasting patients, even when the emotional factor is disregarded, do not indicate the constant occur-rence of a fasting hyperglycemia in hyperthyroidism.

In Table 3 are presented the results obtained in a series of experi-ments in which blood sugar was determined in seventeen hyperthyroid

TABLE 3.—BLOOD SUGAR DETERMINATIONS IN HYPERTHYROID—

Lab. No.	Date of Experiment	Blood Sugar, per Cent.					Urine Sugar, per Cent.*			
		Fasting	1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	Fasting	2 Hrs.	4 Hrs.	6 Hrs.
121	12/18	0.114	0.154	0.091	0	+	+	0
121	1/5	0.080	0.126	0.115	0	+?	+?	+?
111	11/25	0.100	0.108	0.140	0	2.4	0	0
125	12/21	0.107	0.133	0.095	0	+	+?	+?
125	1/14	0.100	0.184	0.153	0	+	+	+
125	2/14	0.105	0.134	0.137	0.120	0	+?	0	0
161	3/21	0.114	0.204	0.156	0.096	+?	0.8	0.4	0.2
137	2/7	0.125	0.105	0.190	0.110	0	+	+	+
137	3/16	0.112	0.153	0.112	0.089	0	+?	+?	0
83	10/5	0.114	0.125	0	+++	+
83	10/9	0.133	0.171	0.130	0	0	0	0
83	11/27	0.104	0.124	0.095	0	0.4	0.3	0
83	11/20	0.101	0.117	0.087	0	0	0	0
88	10/18	0.084	0.152	+	4.1	0.8	0.4
88	12/12	0.117	0.091	0	3.1	+	+
106	11/15	0.100	0.140	0.116	0	1.3	1.5	0.9
106	12/10	0.087	0.097	0	0.2	+	0
129	1/15	0.099	0.181	0.134	0	0.54	0.3	+
126	1/6	0.091	0.200	0.108	0.083	0	0.9	+	0
126	2/13	0.127	0.165	0.148	0.091	0	0	+?	+?
117	11/25	0.130	0.170	0.100	0	1.3	0	0
117	12/11	0.100	0.110	0.100	0	0.2	+	0
131	1/17	0.091	0.090	0.077	0	0	0	0
100	11/3	0.091	0.194	0.135	0	2.7	1.4	0.3
135	1/30	0.108	0.164	0	+	0	0
135	2/5	0.075	0.232	0.164	0.069	0	1.4	0.6	+
93	1/15	0.080	0.188	0.133	0.124	0	+	+	0
110	11/18	0.110	0.220	0.080	0	2.5	0.2	+?
110	12/11	0.110	0.200	0.099	0	4.0	1.2	1.6
68	2/20	0.096	0.200	0.145	0.094	0	1.1	+?	+?
143	2/14	0.095	0.160	0.102	0.094	0	+?	0	0

PATIENTS AFTER INGESTING GLUCOSE AND BREAD

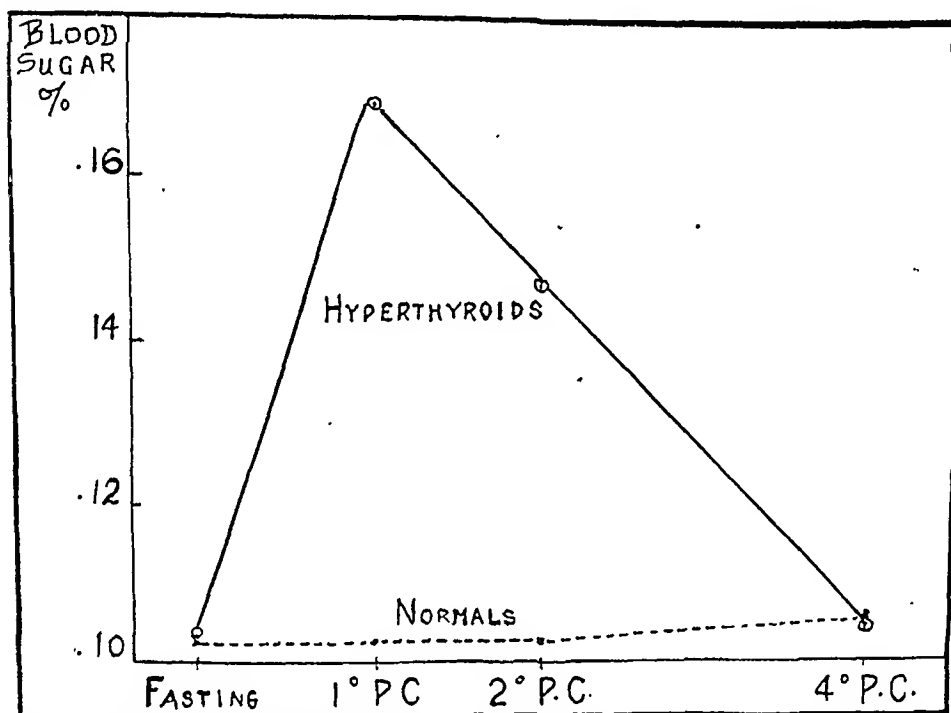
Pulse	Weight, Kg.	Basal Metabolism per Cent. Variation from Normal	Remarks
131	57.0	Dec. 16 +109	Woman, aged 21 years. Very toxic; not excited
116	55.5	+84	After complete rest for one month; not excited
129	38.5	+83	Woman, aged 55 years. Very toxic
133	53.0	Dec. 18 +91, Dec. 26 +61	Woman, aged 27 years. Very toxic
108	63.0	Jan. 11 +65, Jan. 19 +50	Somewhat improved
96	52.7	+36	Ligated January 19; lobectomy January 20; somewhat improved
126	46.4	Mar. 29 +84	Woman, aged 26 years. Toxic
112	53.0	+71	Man, aged 35 years. Very toxic.
87	49.5	+31	Lobectomy March 5. Much improved
127	49.9	+56	Man, aged 22 years. Very toxic
96	52.0	+36	Man, aged 22 years. Very toxic
97	45.5	+30	Partial thyroidectomy October 16
81	43.6	+ 8	Very much improved
141	54.7	+54	Woman, aged 22 years. Very toxic
127	51.1	+29	Vessels ligated November 2; partial thyroidectomy November 17
112	37.5	+50	Woman, aged 41 years. Intrathoracic goiter; mildly toxic
82	38.0	+ 7	Partial thyroidectomy November 24; very much improved
145	47.7	+49	Man, aged 39 years. Fairly severe case
122	49.3	+47	Woman, aged 34 years. Mild case
105	49.3	+19	Lobectomy January 23; much improved
114	46.6	+45	Woman, aged 22 years. Mildly toxic
100	46.8	Dec. 15 +25	Condition improved by complete rest in bed
99	59.0	+42	Woman, aged 33 years. Mild case
149	51.1	+41	Woman, aged 41 years. Under treatment by prolonged rest and Roentgen ray
122	53.2	+39	Woman, aged 39 years. Mild case; somewhat excited by venipuncture
106	53.7	+22	Improved under treatment by rest in bed; not excited
125	53.5	+38	Woman, aged 33 years. Mild thyrotoxicosis; after treatment by complete rest
96	56.8	+34	Woman, aged 39 years. Mild thyrotoxicosis; much excited by venipuncture
108	54.7	Dec. 18 +42, Dec. 3 +35	Not excited by venipuncture
81	54.0	Feb. 17 +37, Feb. 25 +31	Woman, aged 35 years. Toxic
104	54.1	+27	Woman, aged 36 years. Mild case after treatment by prolonged rest

* The symbol + is used to indicate a positive sugar test in cases in which the amount of sugar present was too small to be determined quantitatively (less than 0.2 per cent.). The symbol +? was used to indicate the fact that with Benedict's reagent we obtained only the greenish color which undoubtedly indicated the presence of small amounts of reducing sugar, but which is, as a rule, disregarded in most clinical laboratories.

patients before, and at intervals of one, two and four hours after the ingestion of 100 gm. of glucose and 50 gm. of bread.

In a number of these cases we have been able to repeat the test during the course of treatment (by rest) or after operation.

An inspection of the results given in Table 3 confirms the impression created by the experiments of Table 2, which have already been discussed; that is, that fasting hyperglycemia is of rare occurrence in hyperthyroidism. Alimentary hyperglycemia lasting in some cases for four hours after the ingestion of carbohydrate is, however, invariably present.



The average blood sugar curves of hyperthyroid cases and normals after the ingestion of 100 gm. glucose and 60 gm. bread.

The average curves for blood sugar after the ingestion of our test breakfast by the normal subjects and by the hyperthyroid cases have been plotted on the chart and show strikingly the difference in behavior of the two classes of subjects.

Clinically, it has been observed that thyroid administration frequently causes the subject to show an alimentary glycosuria. The experiments of Cramer and Krause,¹² in which it was shown that the administration of thyroid to rats and cats caused almost complete disappearance of glycogen from the liver, would seem to explain the frequent occurrence of glycosuria in hyperthyroidism as due to a lack

12. Cramer, W., and Kranse, R. A.: Proc. Roy. Soc., London, 1913, 86, 550.

of ability on the part of the patient to store ingested carbohydrate. On this assumption, if in addition we assume that the increase in basal metabolism gives a measure of the excess of thyroid secretion, it would follow that in cases in which the basal metabolism is high, alimentary hyperglycemia and glycosuria should also be more readily induced and of a more severe type. Our results do not, however, confirm this hypothesis.

The cases are arranged in order of severity as measured by the percentage variation from normal of the basal metabolism, and it is at once apparent that it is impossible in this series of cases to trace any relation between the severity of the symptoms and the degree of alimentary hyperglycemia. There is also no apparent relation between the severity of intoxication and the degree of glycosuria. In a number of cases it was possible to repeat the experiment after the patient's condition had been improved by rest or by operation, and, as will be noted, in practically all these cases the alimentary hyperglycemia produced by our test meal is less severe in this second test than that obtained in our first observation. In the discussion of our results it is impossible to overlook the possibility of the existence of "emotional" hyperglycemia and glycosuria. Hyperthyroid patients are notorious examples of nervous instability, and it is conceivable that in some of our experiments the emotional factor was involved. We have observed, however, that while the last venipuncture invariably caused the greatest annoyance, the average values for the fasting blood sugar and for the determination made four hours after breakfast are usually almost identical. Thus, Patient 88 was much excited by the second experiment and comparatively calm during the first, yet the blood sugar value is lower on the former test than on the latter. Similarly, Patient 110 was much excited by the first series of venipunctures, but quite placid during the second test; the sugar curve is, however, similar in both observations.

A few observations are to be found in the literature which indicate that in hypothyroid cases the fasting blood sugar figures are considerably below normal, but may be increased by the administration of thyroid. While the foregoing work has been in progress, two cases of hypothyroidism have come under observation, and in view of the small number of observations so far published on this subject it has seemed worth while to present our results.

CASE 1.—A woman, aged 24, weight 53 kg., had myxedema, together with heart block.

First observation, Nov. 6, 1916: At this time the patient had been taking 26 to 28 grains of thyroid extract per day for a period of five weeks. Blood sugar (fasting) was 0.086 per cent.; basal metabolism, per cent. of normal, + 47.

Second observation, Nov. 20, 1916: All thyroid indications stopped four

days before. Blood sugar (fasting) was 0.090 per cent.; basal metabolism, per cent. of normal, ± 28 .

CASE 2.—A woman aged 20, weight 39.5 kg., with symptoms of cretinism. First observation, Feb. 15, 1917: There was no thyroid medication. Blood sugar (fasting) was 0.11 per cent.; blood sugar two hours after 100 gm. glucose, 0.10 per cent.; basal metabolism, per cent. variation from normal, -17 .

Second observation, March 13, 1917: After 4 grains of thyroid per day for twenty days, then 1 grain per day for seven days, the blood sugar (fasting) was 0.10 per cent.; blood sugar one hour after 100 gm. glucose, 0.11 per cent.; blood sugar, two hours after 100 gm. glucose, 0.11 per cent.; basal metabolism, per cent. variation from normal, $+5$.

The above results fail to show any marked effect produced on blood sugar by the administration of thyroid, but in view of the small number of cases it seems scarcely justifiable to draw conclusions from these experiments.

SUMMARY

Fasting hyperglycemia is of extremely rare occurrence in hyperthyroidism. Alimentary hyperglycemia (following the administration of 100 gm. of glucose and 50 gm. of bread) was, however, observed in every case examined.

No relation could be found between the degree of hyperglycemia and the intensity of glycosuria; neither was it possible to obtain any evidence of a relation between the severity of intoxication (as measured by the percentage increase over normal of the basal metabolism) and the occurrence of hyperglycemia. In a number of cases it was found, however, that after improvement of the patient's condition by rest or by operation the alimentary hyperglycemia was of a much lower grade than that induced by the same test meal given before treatment.

In two cases of hypothyroidism no change in the fasting blood sugar level was observed to result from the administration of thyroid extract.

INDEX TO VOLUME XX

	PAGE
Abramson, H. L.: A study of poliomyelitis. Report of the work of the meningitis division of the research laboratory in the 1916 epidemic.....	341
Acidosis, studies on; the immediate cause of death, and remarks on the acidosis of nephritis; James L. Whitney.....	931
Alexander, H. L.: Asthma complicating serum treatment of pneumonia...	636
Amyotonia congenita of Oppenheim. Report of six cases, with full review of the literature; Mark S. Reuben.....	657
Anemia, influence of splenectomy on metabolism in; W. Denis.....	79
Anemia, severe, with elongated and sickle-shaped red blood corpuscles, study of erythrocytes in case of; V. E. Emmel.....	586
Arthritis, acute, a report on forty cases of, treated by the intravenous injection of foreign protein; Russell L. Cecil.....	951
Asthma complicating serum treatment of pneumonia; H. L. Alexander....	636
Aub, J. C.: Blood sugar in hyperthyroidism.....	964
Auricular flutter. A consideration of some problems arising in the study of a case and of the literature. D. Heard and A. E. Strauss.....	409
Barker, B. I.: Clinical studies on the respiration. V. The basal metabolism and the minute-volume of the respiration of patients with cardiac disease.	468
Barringer, Theodore B., Jr.: Studies of the heart's functional capacity.....	829
Basal metabolism and the minute-volume of the respiration of patients with cardiac disease. Clinical studies on the respiration; F. W. Peabody, J. A. Wentworth and B. I. Barker.....	468
Beriberi, blood in, studies of; I. Yoshikawa, K. Yano and T. Nemoto.....	103
Blood coagulation. I. Studies in protein intoxication; H. F. Shattuck.....	167
Blood, human, remarks on cholesterol content of; F. D. Gorham and V. C. Myers	599
Blood picture, a case of cantharides poisoning with special reference to the; Samuel T. Lipsitz and A. J. Cross.....	889
Blood sugar in hyperthyroidism; W. Denis and J. C. Aub, with the assistance of A. S. Minot.....	964
Blood sugar, studies on; Louis Hamman and I. I. Hirschman.....	761
Bookman, A.: A study of renal function in patients convalescing from acute fevers	112
Book Reviews:	
A monograph on the epidemic of poliomyelitis (infantile paralysis) in New York City in 1916.....	479
Pathogenic micro-organisms; William Hallock Park and Anna Wessels Williams, assisted by Charles Krumweide, Jr.....	828
The diagnosis and treatment of myocardial function, with special reference to the use of graphic methods. L. S. Hart.....	480
Bredeck, J. F.: Ventricular fibrillation in man with cardiac recovery.....	725
Burge, W. E.: The effect of pancreatectomy on the catalase content of the tissues	892
Burrows, H. T.: The study of a small outbreak of poliomyelitis in an apartment house, occurring in the course of an epidemic in a large city....	56
Campbell, Walter R.: Observations on acute mercuric chlorid nephrosis, with a report of two cases.....	919
Cantharides poisoning with special reference to the blood picture; Samuel T. Lipsitz and A. J. Cross.....	889

	PAGE
Cantharides, tincture of, polycythemia induced by; preliminary report; Samuel T. Lipsitz, A. L. Fucrth and A. J. Cross.....	913
Cardiac disease, basal metabolism and the minute-volume of the respiration of patients with. Clinical studies on the respiration, V; F. W. Peabody, J. A. Wentworth and B. I. Barker.....	468
Cardiac pacemaker, temperature method in localization of; B. H. Schlomovitz and C. S. Chase.....	613
Catalase content of tissues, the effect of pancreatectomy on the; J. Kennedy and W. E. Burge.....	892
Cecil, Russell L.: A report on forty cases of acute arthritis treated by the intravenous injection of foreign protein.....	951
Chase, C. S.: Temperature method in localization of cardiac pacemaker.....	613
Cholesterol content of human blood, remarks on; F. D. Gorham and V. C. Myers	599
Christie, C. D.: Study of a case of diabetes insipidus with special reference to the mechanism of the diuresis and of the action of the pituitary extract on it.....	10
Crohn, B. B.: Studies in the variations of the tonus of the gastric musculature in health and disease.....	145
Cross, A. J.: A case of cantharides poisoning with special reference to the blood picture.....	889
Cross, A. J.: Polycythemia induced by tincture of cantharides.....	913
Crowder, Joseph R.: Five generations of angioneurotic edema.....	840
Crowder, Thomas R.: Five generations of angioneurotic edema.....	840
Denis, W.: Blood sugar in hyperthyroidism.....	964
Denis, W.: Influence of splenectomy on metabolism in anemia.....	79
Denis, W.: The nonprotein constituents of edema fluids.....	879
Diabetes insipidus, study of case of, with special reference to the mechanism of the diuresis and of the action of pituitary extract on it; C. D. Christie and G. N. Stewart.....	10
Diabetes mellitus, observations on kidney function in; R. Fitz.....	809
Diabetics, study of the influence of low diets, or the Allen method of treatment, on the physical vigor of. Effect of undernutrition on muscular force; J. R. Williams.....	399
Diagnostic signs from the scaleni, intercostal muscles and diaphragm in lung ventilation; C. F. Hoover.....	701
Dyspituitarism, multiple hemangiomas of the skin associated with; G. D. Head	24
Dyspnea, a mechanical factor in the production of, in patients with cardiac disease. Clinical studies on the respiration. III; F. W. Peabody.....	433
Dyspnea, the vital capacity of the lungs and its relation to. IV. Clinical studies on the respiration; F. W. Peabody and J. A. Wentworth.....	443
Edema, angioneurotic, five generations; Joseph R. Crowder and Thomas R. Crowder	840
Edema fluids, the nonprotein constituents of; W. Denis, with the assistance of A. S. Minot.....	879
Electrocardiogram, an error in, arising in the application of the electrodes; H. E. B. Pardee.....	161
Electrocardiogram; its relation to cardiodynamic events; C. J. Wiggers... ..	93
Emetin diarrhea—clinical and experimental; A. R. Kilgore and J. H. Lieu..	178
Emmel, V. E.: Study of erythrocytes in the case of severe anemia with elongated and sickle-shaped red blood corpuscles.....	586
Erythrocytes in case of severe anemia with elongated and sickle-shaped red blood corpuscles, study of; V. E. Emmel.....	586

Ferment-antiferment balance and its relation to therapeutics; W. F. Petersen.	515
Fishberg, Maurice; Localized and interlobar pneumothorax complicating pulmonary tuberculosis	739
Fitz, R.: Observations on kidney function in diabetes mellitus.....	809
Fuerth, A. L.: Polycythemia induced by tincture of cantharides; preliminary report	913
Garrison, P. E.: Relation of pellagra to location of domicile in Spartan Mills. S. C., and the adjacent district.....	198
Garrison, P. E.: Relation of pellagra to location of domicile in Inman Mills, Inman, S. C.....	521
Gastric musculature in health and disease, studies in variations of the tonus of; B. B. Crohn and A. O. Wilensky.....	145
Gekler, W. A.: Phthisis pulmonalis and other forms of intrathoracic tuberculosis	32
Gorham, F. D.: Remarks on cholesterol content of human blood.....	599
Gout, renal function in; C. W. McClure.....	641
Gout, study of uric acid in; C. W. McClure and J. H. Pratt.....	481
Hamman, Louis: Studies on blood sugar.....	761
Hanzlik, P. J.: The salicylates. VIII. Salicyl edema.....	329
Hart, L. S.: The diagnosis and treatment of myocardial function, with special reference to the use of graphic methods.....	480
Head, G. D.: Multiple hemangiomas of the skin associated with dyspituitarism	24
Heard, J. D.: Auricular flutter. A consideration of some problems arising in the study of a case, and of the literature.....	409
Heart block associated with high blood pressure; J. H. Musser, Jr.....	127
Heart's functional capacity, studies of the; Theodore B. Barringer, Jr.....	829
Hemangiomas, multiple, of the skin associated with dyspituitarism; G. D. Head	24
Hemochromatosis, iron metabolism of; C. P. Howard and F. A. Stevens....	896
Hewlett, A. W.: The pulse flow in the brachial artery. V. The influence of certain drugs	1
Hirschman, I. I.: Studies on blood sugar.....	761
Honeij, J. A.: Pyopneumothorax and pneumothorax. Report of two cases with interesting clinical and roentgenologic findings.....	629
Hoover, C. F.: Diagnostic signs from the scaleni, intercostal muscles and the diaphragm in lung ventilation.....	701
Howard, C. P.: The iron metabolism of hemochromatosis.....	896
Hydronephrosis, experimental; N. M. Keith and D. S. Pulford, Jr.....	853
Hyperthyroidism, blood sugar in; W. Denis and J. C. Aub, with the assistance of A. S. Minot.....	964
Iron metabolism of hemochromatosis; C. P. Howard and F. A. Stevens....	896
Keith, N. M.: Experimental hydronephrosis.....	853
Kennedy, J.: The effect of pancreatectomy on the catalase content of the tissues	892
Kidney function in diabetes mellitus, observations on; R. Fitz.....	809
Kilgore, A. R.: Emetin diarrhea—clinical and experimental.....	178
Kitagawa, J.: The etiologic agent of rat bite disease, preliminary report....	317
Leukemic and normal blood, studies on the oxidase reaction of the cells in; N. Rosenthal	184
Lipsitz, Samuel T.: Polycythemia induced by tincture of cantharides; preliminary report	913

	PAGE
Lieu, J. H.: Emetin diarrhea—clinical and experimental.....	178
Lung ventilation, diagnostic signs from the scaleni, intercostal muscles and the diaphragm in; C. F. Hoover.....	701
MacNeal, W. J.: Relation of pellagra to location of domicile in Spartan Mills, S. C., and the adjacent district.....	198
MacNeal, W. J.: Relation of pellagra to location of domicile in Inman Mills, Inman, S. C.....	521
McClure, C. W.: Renal function in gout.....	641
McClure, C. W.: Study of uric acid in gout.....	481
Mehrtens, H. G.: Absorption of phenolsulphonephthalein from subarachnoid space in diseases of central nervous system.....	575
Mercuric chlorid nephrosis, acute, observations on, with a report of two cases; Walter R. Campbell, Toronto, Canada.....	919
Minot, A. S.: Blood sugar in hyperthyroidism.....	964
Minot, A. S.: The nonprotein constituents of edema fluids.....	879
Mukoyama, T.: The etiologic agent of rat bite disease.....	317
Musser, J. H., Jr.: Heart block associated with high blood pressure.....	127
Myers, V. C.: Remarks on cholesterol content of human blood.....	599
Myocardial function, diagnosis and treatment of, with special reference to the use of graphic methods. Book review; L. S. Hart.....	480
Neal, J. B.: A study of poliomyelitis. Report of the work of the meningitis division of the research laboratory in the 1916 epidemic.....	341
Nemoto, T.: Studies of the blood in beriberi.....	103
Nephritis, acidosis of, the immediate cause of death, and remarks on; studies on acidosis; James L. Whitney.....	931
Nephrosis, acute mercuric chlorid, observations on, with a report of two cases; Walter R. Campbell.....	919
Nonprotein constituents of edema fluids; W. Denis, with the assistance of A. S. Minot.....	879
Oxidase reaction of the cells in normal and leukemic blood, studies on; N. Rosenthal	184
Pancreatotomy on the catalase content of the tissues, effect of; J. Kennedy and W. E. Burge.....	892
Pardee, H. E. B.: An error in the electrocardiogram arising in the application of the electrodes.....	161
Park, E. A.: The study of a small outbreak of poliomyelitis in an apartment house, occurring in the course of an epidemic in a large city.....	56
Park, William Hallock: Pathogenic micro-organisms; book review.....	828
Pathogenic micro-organisms; book review; William Hallock Park and Anna Wessels Williams, assisted by Charles Krumweide, Jr.....	828
Peabody, F. W.: Clinical studies on the respiration. III. A mechanical factor in the production of dyspnea in patients with cardiac disease....	433
Peabody, F. W.: Clinical studies on the respiration. IV. The vital capacity of the lungs and its relation to dyspnea.....	443
Pellagra, relation of, to location of domicile in Spartan Mills, S. C., and the adjacent district; J. F. Siler, P. E. Garrison and W. J. MacNeal....	198
Pellagra, relation of, to location of domicile in Inman Mills, Inman, S. C.; J. F. Siler, P. E. Garrison and W. J. MacNeal.....	521
Petersen, W. F.: Ferment-antiferment balance and its relation to therapeusis	515
Petersen, William F.; Serum changes following protein "shock" therapy....	716
Phthisis pulmonalis and other forms of intrathoracic tuberculosis; W. A. Gekler	32

Phenolsulphonephthalein, absorption of from subarachnoid space in diseases of central nervous system; H. G. Mehrrens and H. F. West.....	575
Pituitary extract, action of, and mechanism of diuresis, in diabetes insipidus; C. D. Christie and G. N. Stewart.....	10
Pneumonia, asthma complicating serum treatment of; H. L. Alexander.....	636
Pneumothorax, localized and interlobar, complicating pulmonary tuberculosis; Maurice Fishberg.....	739
Poliomyelitis, a monograph on the epidemic of, in New York City in 1916; book review	479
Poliomyelitis, study of. Report of the work of the meningitis division of the research laboratory in the 1916 epidemic; J. B. Neal, L. Abramson and associates	341
Poliomyelitis, study of a small outbreak of, in an apartment house, occurring in the course of an epidemic in a large city; M. T. Burrows and E. A. Park	56
Polycythemia induced by tincture of cantharides; preliminary report; Samuel T. Lipsitz, A. L. Fuerth and A. J. Cross.....	913
Pratt, J. H.: Study of uric acid in gout.....	481
Protein, foreign, a report on forty cases of acute arthritis treated by the intravenous injection of; Russell L. Cecil.....	951
Protein intoxication, studies in. I. Blood coagulation; William F. Petersen.	716
Protein "shock" therapy, serum changes following; William F. Petersen....	716
Pulford, D. S., Jr.: Experimental hydronephrosis	853
Pulse flow in the brachial artery. V. Influence of certain drugs; A. W. Hewlett	1
Pyopneumothorax and pneumothorax. Report of two cases with interesting clinical and roentgenographic findings; J. A. Honcij.....	629
Rat-bite disease, etiologic agent of; preliminary report; J. Kitagawa and T. Mukoyama	317
Renal function in patients convalescing from acute fevers, study of; A. Bookman	112
Renal function in gout; C. W. McClure.....	641
Respiration, clinical studies on. III. A mechanical factor in the production of dyspnea in patients with cardiac disease; F. W. Peabody.....	433
Respiration, clinical studies on. IV. The vital capacity of the lungs and its relation to dyspnea; F. W. Peabody and J. A. Wentworth.....	443
Respiration, clinical studies on. V. The basal metabolism and the minute-volume of the respiration of patients with cardiac disease; F. W. Peabody, J. A. Wentworth and B. I. Barker.....	468
Reuben, Mark S.: Amyotonia congenita of Oppenheim. Report of six cases, with a full review of the literature.....	657
Reycraft, J. L.: The salicylates. VIII. Salicyl edema.....	329
Robinson, G. Canby: Ventricular fibrillation in man with cardiac recovery.	725
Rosenthal, N.: Studies on the oxidase reaction of the cells in normal and leukemic blood	184
Salicyl edema, the salicylates. VIII; P. J. Hanzlik, R. W. Scott and J. L. Reycraft	329
Salicylates, the. VIII. Salicyl edema; P. J. Hanzlik, R. W. Scott and J. L. Reycraft	329
Schick test; further studies with; A. Zingher.....	392
Schlomovitz, B. H.: Temperature, method in localization of cardiac pacemaker	613
Scott, R. W.: The salicylates. VIII. Salicyl edema.....	329
Serum changes following protein "shock" therapy; William F. Petersen...	716
Shattuck, H. F.: Studies in protein intoxication. I. Blood coagulation....	167

	PAGE
Siler, J. F.: Relation of pellagra to location of domicile in Spartan Mills, S. C., and the adjacent district.....	198
Siler, J. F.: Relation of pellagra to location of domicile in Inman Mills, Inman, S. C.....	521
Splenectomy, influence of, on metabolism in anemia; W. Denis.....	79
Stevens, F. A.: The iron metabolism of hemochromatosis.....	896
Stewart, G. N.: Study of a case of diabetes insipidus with special reference to the mechanism of the diuresis and of the action of pituitary extract on it	10
Strauss, A. E.: Auricular flutter. A consideration of some problems arising in the study of a case, and of the literature.....	409
Subarachnoid space, absorption of phenolsulphonephthalein from, in diseases of central nervous system; H. G. Mehrtens and H. F. West.....	575
Temperature method in localization of cardiac pacemaker; B. H. Schlomovitz and C. S. Chase.....	613
Tuberculosis, pulmonary, localized and interlobar pneumothorax complicating; Maurice Fishberg.....	739
Undernutrition, effect of, on muscular force. Study of influence of low diets, or the Allen method of treatment, on the physical vigor of diabetics; J. R. Williams.....	399
Uric acid in gout, study of; C. W. McClure and J. A. Pratt.....	481
Ventricular fibrillation in man with cardiac recovery; G. Canby Robinson and J. F. Bredeck.....	725
Wentworth, J. A.: Clinical studies on the respiration. IV. The vital capacity of the lungs and its relation to dyspnea.....	443
Wentworth, J. A.: Clinical studies on respiration. V. The basal metabolism and the minute-volume of the respiration of patients with cardiac disease	468
West, H. F.: Absorption of phenolsulphonephthalein from subarachnoid space in diseases of central nervous system.....	575
Whitney, James L.: The immediate cause of death, and remarks on the acidosis of nephritis; studies on acidosis.....	931
Wiggers, C. J.: The electrocardiogram; its relation to cardiodynamic events	93
Wilensky, A. O.: Studies in the variations of the tonus of the gastric musculature in health and disease.....	145
Williams, Anna Wessels: Pathogenic micro-organisms; book review.....	828
Williams, J. R.: Effect of undernutrition on muscular force. A study of the influence of low diets, or the Allen method of treatment, on the physical vigor of diabetics.....	399
Yano, K.: Studies of the blood in beriberi.....	103
Yoshikawa, I.: Studies of the blood in beriberi.....	103
Zinger, A.: Further studies with the Schick test.....	392

